P H E N Y L K E T O N U R I A

A Clinical and Genetic Study of British Families.

Thesis for M.D. Degree

Submitted by

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I. INTRODUCTION

Previous Work.

In 1934, Følling in Norway reported on the excretion of phenylpyruvic acid in the urine of several persons suffering from mental defect. This metabolic anomaly had not been described before in man, and, as it has never been found in the urine of normal persons, Følling thought it very likely that there was a connection between the chemical abnormality and imbecility. He called the disease "imbecillitas phenyl-pyruvica".

Følling's interesting discovery that an inborn error of metabolism is always associated with mental deficiency has not as yet proved as great a stimulus to psychiatric research as might have been expected, possibly because the abnormality is rare. Penrose was the first to follow up Følling's work. In 1935 (Penrose 1935 a) he found an affected brother and sister in the Royal Eastern Counties' Institution at Colchester, and on the basis of the familial incidence of this rare constitutional disorder, with unaffected parents, he thought that, like alcaptonuria, it was probably inherited as a single Mendelian recessive character. The hypothesis of recessive inheritance was much strengthened when, later in 1935, Penrose (1935 b) found the chemical abnormality in another family at Colchester which he had previously published (Penrose 1934) as a clear example of the mode of action of a rare recessive gene. In this family there were two cousin marriages with affected offspring from both. The parental consanguinity, the familial incidence among the sibs, and unaffected parents argued strongly for recessivity. Penrose and Quastel of Cardiff who had

therapeutic possibilities in the insanities that good evidence for its truth must be produced before one can begin hopefully on the large amount of experimental work and of attempts at treatment which the hypothesis would demand.

Yet the interest of phenylketonuria does not cease here. One of our patients at Colchester died, and at the post mortem examination at which I was present, small neurofibromata were found upon all the nerves of the body. This case was published by Penrose, 1939.

In 1937, Jervis in America published a clinical and biochemical and genetic investigation of fifty cases of "phenylpyruvic oligophrenia" and later, Jervis 1939, he published a genetic analysis of 125 New England families containing 213 cases. The only other clinical paper on this disorder is that by Bates who described three patients he found at Stoke Park Colony, Bristol. I investigated the families of these patients, and with Dr Bates' kind permission, I also examined the patients. I have included them in this survey. I shall review these papers when I describe my own material.

Phenylketonuria is rare. But it seemed to me that the disorder was interesting enough to make it worth while collecting a moderately large number of examples. Følling's original paper described ten cases and Penrose had recorded two families. The symptomatology, the course and the outcome of the disease were of course only inadequately known. Its sex incidence, the range of severity of the mental deficiency and the nature of the associated anomalies were unknown. It was important to find out if the disease could

be diagnosed on clinical signs apart from the urinary abnormality. One also wanted to know if neurofibromatosis was only a rare accompaniment or if it occurred in other cases. The hypothesis of recessive inheritance required confirmation, and it was of great theoretical importance to investigate the incidence of psychoses among the relatives.

Method of Collecting Material.

(a) The Patients. The search for examples of a rare disease calls for the cooperation of many people, and I am greatly indebted to the Medical Superintendents and other members of the staffs of Institutions and Mental Hospitals in several parts of England and of Scotland, who so kindly searched for the abnormality among patients in their charge and told me of their findings. The affected patients were discovered not on clinical grounds but by examining the urines of large numbers of mental defectives. The test used is a simple one; the appearance of a bright green colour on adding ferric chloride to the urine indicates phenylketonuria.

In particular I am indebted to Dr L.S.Penrose at Colchester, Dr R.M.Stewart of Leavesden, Dr Lindsay at Caterham, Dr Steward in Surrey, Dr Berry and Dr Bates at Stoke Park, Bristol, Dr Richard Eager in Devon, Captain Mayer at the Royal Western Counties' Institution, Starcross, the Head Deaconess at Exeter, Dr O'Keefe at Cornwall Mental Hospital, Dr Hennelly and Dr Quastel at Cardiff Mental Hospital, Dr Lewis at Hensol Castle, Glamorgan, Dr Parfitt at Warwick, Dr Brookes-Keith in Suffolk,

Dr Saxty Good at Oxford City and County Mental Hospital, Dr Robertson at Calderstones and Dr Rose at Brockhall, Lancashire, Dr Chislett at Lennox Castle, Glasgow, Dr Anderson at Montrose, Dr Forbes at Baldovan Institution, Dundee, Dr Bailey at Gogarburn, Edinburgh and Dr Spence at the Royal Scottish National Institution. This survey probably includes most of the phenylketonurics as yet discovered in Britain . (By April 1940 a few more examples of phenylketonuria had been found at Stoke Park, some at Caterham, and one more at Brockhall. Dr Forbes at Baldovan had found two cases.)

I began with the three families which had affected members in the Royal Eastern Counties' Institution at Colchester. I have included in the survey the two families previously published by Penrose. I have, of course, investigated these families for myself, and they are recorded here with some amendments and additions. While making a survey of certain types of psychoses in various parts of the country, I took the opportunity to search for cases of phenylketonuria. I found two affected sisters at the Oxford Mental Hospital,. While in Devon I was able to test for myself the urines of more than 500 defectives at the Royal Western Counties' Institution at Starcross, where I found one affected person. I also examined the patients in several other homes and Public Assistance Institutions in Devon. In the Home of the Holy Innocents at Exeter, where only very helpless defectives of severe type are looked after, I found no less than three examples of phenylketonuria among 45 children. I saw the patients whom Dr Quastel has found in Cardiff and also several patients at Stoke Park, including the three which are the subject of Dr Bates' paper. I found other cases among the relatives of these patients. Later I investigated the 19 patients which

Dr Robertson and Dr Rose had found in Lancashire, and also the four patients whom Dr Spence had in the Royal Scottish National Institution at Larbert.

I first examined the affected patient in the Institution, and then visited the relatives. Difficulties in finding and in approaching the relatives were greatly lessened by the cooperation of the various associations interested in mental deficiency. In particular Miss MacMichael of the Devon Voluntary Association, Mrs M'cCann and Miss Andrew of the Lancashire Associations for Mental Welfare gave me useful information as to the whereabouts of the relatives, arranged interviews which otherwise might have been impossible, and in many other ways saved much of my time. The Research Department's social investigator, Miss Newlyn, in some cases made a preliminary survey of the families, and I am much indebted to her for her tactful approach and preparation.

In all possible cases, I saw the parents in their own home and heard their story of their child's illness. Such a history has often to be taken with care. Parents sometimes produce quite unintentional retrospective falsifications of the child's early history, which have the effect of "explaining", and thus in some way mitigating, the tragedy of their child's life. Sometimes these falsifications are more subtle than the simple, obvious and frequent remark that "the child fell on its head, and ever since then" was defective. A parent may confidently volunteer that the child had "epileptic fits" in infancy, and yet on closer questioning it may be difficult to obtain a history of seizures of any kind. A parent may forget to mention important facts until prompted by leading questions. This decreases the value of the history.

These circumstances take on additional importance when one is investigating the symptomatology of a new disease, and does not know what facts may be significant. In taking the patient's history one has to compromise between asking about all sorts of possible and improbable events (and so boring or annoying the parents) and yet making a reasonably complete survey of the patient's life. Another impeding factor was that the families I investigated were scattered throughout England and Scotland, and so it was not possible to revisit them at a later date for new enquiries. I have tried to err rather on the side of omitting historical details which, though interesting, had possibly little basis in fact. My analysis of the symptomatology of phenylketonuria differs in several important respects from that of Jervis. Further studies will be required before the clinical picture of the disease becomes well established.

(b) The Families. Whenever possible I examined the parents mentally and physically and also as many of the brothers and sisters of the patient as I could conveniently see. I paid particular attention to these near relatives, and obtained information about date of birth, past medical history and present health. I also inquired particularly about miscarriages and stillbirths. I obtained specimens of urine from these relatives.

I tried always to obtain family history not only from the parents but also from at least one more distant relative. I visited the grandparents, uncles and aunts and first cousins, inquiring about age and mental and bodily health. In many families more distant relatives were also recorded. I was able to examine all relatives who were in a mental or general hospital, and I received

much information from the family physicians and from hospital records. Special enquiries were made about consanguineous marriages, and also about the parents racial ancestry. The parents and sibships are fully recorded in Appendix I, and the more distant relatives in Appendix III. Clinical notes on the cases of phenylketonuria and on all abnormal relations are given in Appendix II. Family charts are given in Appendix IV.

As far as possible I obtained a few drops of blood from the parents and sibs for determination of the blood-group. The specimens of blood were sent by post to the Galton Laboratory, London, where Dr G.L.Taylor and his colleagues determined the blood-groups according to the A_1, A_2, B O and MN series. I have included the record of the blood-groups with the parents and sibships in Appendix I. This material forms the basis of a joint paper with Dr Penrose and Dr Taylor on the search for genetic linkage between the gene for phenylketonuria and the A B O and M N allelomorphs. In this case linkage is doubtful. The search for genetic linkage involves the cooperation of workers in different branches of science. It is therefore rather costly and time-consuming. Yet if the aim of human genetics to draw the chromosome map of man is ever to be achieved at some future date such studies must not be neglected. Once a few linkages have been determined the chances of finding others within man's 48 chromosomes will be increased.

In almost all families the relatives were friendly and cooperative. Many parents were pleased that their child was the subject of special investigation. I was often surprised to find that within an hour of arriving in some rural hamlet or industrial slum I should have been allowed to examine and to obtain specimens of blood and urine from parents and children.

Table I.

Incidence of Phenylketonuria
among Mental Defectives in Institutions.

Institution.	Low Grade Patients.		High Grade Patients.	
	Phenyl-ketonuria.	Total Number.	Phenyl-ketonuria.	Total Number.
R. E. C. I. Essex	3	404	0	502
R. W. C. I. Devon	1	69	0	480
Stoke Lyne, Devon	0	47		
Axminster, Devon	0	89		
Calderstones, Lancs.	16	937		
Brockhall, Lancs.	2	368	1	351
Lennox Castle, Scotland	0	56		
Larbert, Scotland	4	218		
Gogarburn, Edinburgh	0	170	0	300
Cornwall Mental Hospital	1	54		
Church Home, Exeter	3	45		
All Institutions	30	2457	1	1633
Percentage phenylketonuric	1.22		0.06	

The investigation of the families took me over a wide area of Britain from Aberdeen to a Cornish village near Penzance, and was a delightful and informative experience. I saw examples of life in the docks of Cardiff and Liverpool, and I obtained comments on affairs from Devon farmers and Cotswold labourers, from a Covent Garden porter in his London home, from the curiously cheerful folk who live in the industrial gloom of Widnes, of Wigan and Warrington, from people in the slums of Manchester, and in the beauty of the Vale of Evesham, and from workers who live the hard life of the Scottish industrial belt.

II. INCIDENCE OF PHENYLKETONURIA

In estimating the incidence of phenylketonuria it is better to leave out those cases whose discovery depended on some special selection or chance finding. I have accordingly based my estimation only on the survey made in Institutions in which the patients were examined ward by ward, taking care not to omit patients from whom it was difficult to get specimens of urine. Table I shows that phenylketonuria occurs in rather more than 1% of low grade defectives of idiot and imbecile grade, but is much less common among the feeble minded, in whom its incidence is about 6 in ten thousand. Unfortunately there are no other quite relevant figures with which I can compare these. However, it is clear that in British Institutions phenylketonuria is about 20 times more frequent among low grade defectives than among high grade defectives. Jervis in his first paper found 42 cases among

8043 defectives of all grades (0.52%) , and in his later paper, 161 cases among 20,300 defectives (0.79%). The incidence in my material among defectives of all grades in Institutions is 31 in 4090, or 0.76%. According to E.O.Lewis (1929) the incidence of all types of mental defect in the general population is 0.734%. From these figures the incidence of phenylketonuria in the general population would be about six per hundred thousand, (0.006%). This incidence is probably too high, because the proportion of patients with severe defect to those with mild defect is much higher inside institutions than in the population outside. Lewis estimated the incidence of imbeciles and idiots in the general population at 0.163%. On this basis, the incidence of phenylketonuria would be 0.163% X 1.22% = 0.002% or two per hundred thousand. This incidence is too low, because it does not include those few phenylketonurics who have relatively slight mental defect. Lewis estimated the incidence of the feeble minded in the general population at 0.592%. If my figure for the incidence of phenylketonuria among the feeble minded, one in 1633, or 0.061%, be taken as approximately correct, then the incidence of phenylketonuria feeble minded persons in the general population is only about four per million. We may therefore say that the incidence of the disease in the general population lies between two and six per hundred thousand, and probably nearer the lower figure than the upper. If we take the rate to be 4 per 100,000, then, on a basis of 40 million population there should be about sixteen hundred (1,600) cases of phenylketonuria in Britain. There are certainly not less than 800, and probably not more than 2400.

The incidence of the disease can also be estimated from the theoretical relationship between parental consanguinity and the frequency of the abnormal gene. Evidence from this source confirms the above incidence, and will be discussed in the section on inheritance. Phenylketonuria is therefore much less rare than alcaptonuria (one in a million), is about as frequent as cystinuria (one in twenty thousand), and is not as frequent as amaurotic idiocy,- three conditions which are also inherited as mendelian recessive characters.

The geographical and racial distribution of this disease has some points of interest. Like amaurotic idiocy, it is apparently less rare in Scandinavia. At Colchester we found only 4 cases in a large institution, Dr Stewart found only 5 at Leavesden, Dr Findlay found none among 1800 at Caterham, and there were none in 520 Surrey patients. It seems that the disease is rare in the Home Counties, but more frequent in the West Country, in Wales and in Lancashire. Although the Scottish National Institution draws most of its patients from neighbouring areas, of the four phenylketonurics found there, only one came from nearby; the other three came from Aberdeen, East Sutherlandshire and the Shetland Isles. Other things being equal, a disease determined by a rare recessive gene will appear particularly in districts where, on account of isolation, inbreeding within the same clan, if not within the same family, is frequent. The classical example of this phenomenon is Sjögren's cases of amaurotic idiocy, which occurred particularly in isolated villages in Sweden. Such an explanation probably holds for phenylketonuria. The rarity of the condition in the home counties may be dependent on the greater mixing of the population there. On the other hand there is no

reason to suppose that the gene for phenylketonuria is not widely scattered throughout the country, indeed throughout the "civilized" world. In the case of 40 of my families, the parents of the phenylketonuric, who each carried the determinating gene, in 24 instances came from the same part of the country, but in 16 instances they came from quite different districts. Examples of the latter type of marriages were between a French Swiss man and a Lancashire woman, between Irish and Welsh, and Scots and Irish. We may therefore expect to find examples of phenylketonuria in all parts of the country, but perhaps rather more frequently in isolated districts. It may be noted in passing that a disease determined by a dominant gene may also appear more frequently in isolated districts, as witness the concentration of Huntington's Chorea in Scotland in the fishing villages of the Moray Firth. The genetical aspects of inbreeding will be discussed in the section on inheritance.

There are no Jewish families in my material, nor in Jervis', although he estimates that 20% of the institution population he tested was of Jewish race. This is in marked contrast to the juvenile form of amaurotic idiocy.

Giossan (1937) found no instances of phenylketonuria among 500 persons suffering from various mental abnormalities, including 27 mental defectives, and suggested, on inadequate grounds, that a racial factor was responsible for the results of Følling and Penrose.

III. SYMPTOMATOLOGY

In his original paper, Følling gave short clinical notes on the four males and six females he found. There were three pairs of brothers and sisters among these ten cases. They were mostly low grade defectives, and at least three were helpless idiots, but it seems that two were imbeciles of rather high grade. Følling observes that "the cases do not form so obvious a group as do cretins or mongols, but there are features which seem, to a certain extent, common to them all". All show a certain rigidity of muscle, a bowed posture and usually a great breadth of shoulder. Only one showed a normal skin. The others showed dryness, roughness, scaling, white papules or chronic eczema.

Jervis, in his first paper, analysed 50 cases and concluded that the disease was clinically a fairly well defined syndrome, consisting of intellectual defect, signs of extrapyramidal disease (rigid posture, muscular hypertonus and hyperkinesias), exaggeration of the deep reflexes, and also characteristic constitutional features, by which he presumably means blond hair, blue eyes and pale, delicate skin, sensitive to sunlight and subject to eczema.

My material consists of 43 families, in which there are 74 undoubted cases of phenylketonuria and a further 12 mentally defective children who died before examination, but who probably were also affected. More than half the phenylketonuric defectives were in institutions but many were being kept at home by their parents.

TABLE II

Sex and Mental Grade of all Phenylketonurics.

	Feeble Minded.	Imbecile.	Idiot.	TOTAL
Male.	3	14	22	39
Female.	3	14	30	47
All Cases.	6	28	52	86

TABLE III

Analysis of Usual Mood of 71 Phenylketonurics

Afraid, apprehensive.	16
Excitable, restless.	16
Not remarkable.	11
Placid.	20
Irritable, angry.	8

There is no doubt that phenylketonuria is always associated with mental defect. I failed to find the chemical abnormality in any parent or sib or other relative of average intelligence. I was able to test the urine of 45 parents and 56 clinically healthy sibs. Følling and Jervis concur in this. Moreover, the urine of the relatives in my families, who suffer from other mental or physical diseases, such as psychoses and endocrine disorders, was not abnormal. I have also examined the urines of more than a thousand mental hospital patients with negative results. Phenylpyruvic acid is not difficult to find, and if it occurred among normal people, it would almost certainly have been discovered before now in the course of the examination of urine for acetone bodies.

The severity of the mental deficiency in my cases, and its relation to sex, are shown in table II Most of the patients are low grade defectives. One third are of imbecile grade, and rather less than two thirds are idiots. Jervis agrees with this. The sexes are about equally affected as regards the severity of the defect. In table II the 12 cases (3 male and 9 female) who died before examination have been classed as idiots because they were apparently severely affected. As might be expected, the proportion of phenylketonurics of feeble minded grade was higher in the cases at home than in those in institutions. The severely affected children tend to come into hospital. (In this thesis the terms idiot, imbecile and feeble minded are used not only in the sense of their legal definitions, but also to indicate intelligence quotients of 0 to 19, 20 to 49, 50 to 69, respectively. Dullards may be taken to have intelligence quotients of 70 to 85, those of average intelligence, 86 to 114, and those of superior intelligence 115 and over).

Jervis produced much evidence that females are more often affected than males, both in the institutional population and in the sibships of his families. My material does not show this. An apparent excess of females might be produced if the disease were more severe in males, so that the males died in infancy or were stillborn, but in my sibships deaths before five years of age were only slightly more frequent in males than in females. (Table VI). Jervis' publication does not allow such an analysis to be made of his material. If there is a real excess of females affected, it is probably not a great excess, as if so it would have shown up in my material.

The clinical histories gave the usual evidence of severe mental deficiency; very delayed and incomplete mental development, inability to control organic reflexes or to speak, and, in the milder cases, the usual inability to learn at school or to hold a job. Other abnormalities were found. The mother's pregnancy and the child's birth were usually said to be normal, but in 8 out of 53 instances the mother had much general ill health, easy fatigue and severe vomiting. In one instance there was uterine haemorrhage in the later months. This incidence of maternal ill health is rather high. Only three births were abnormal: two were premature, and in one instance the child was born in the membranes with an abnormal placenta. In 21 out of 49 instances in which a good history was obtained, the phenylketonuric child suffered from very poor bodily health in infancy. In several instances (13 out of 53) there was a history of disorders of appetite: nine children seemed always ravenous, and four of them craved raw meat, eggs or oranges. As the essence of the biochemical disorder is probably an inability to metabolise at least one of the essential amino acids, the craving for raw meat is interesting. The mother sometimes spontaneously gave a history of severe chronic

No. I. Propositus 2. Female age 44.
Note the pleasant facies, broad shoulders with stoop, fair hair, senile facial wrinkles, wart-like papilloma on nose and eyebrow, moles on neck.

constipation, often requiring enemas. This occurred in 13 out of 55 children. In 25 out of 70 cases a peculiar, abnoxious smell was noticed from the patients, sometimes particularly from the urine and rarely from the faeces.

Følling and Jervis do not mention the smell of their patients. Mr O'Brien, of the Rockefeller Foundation tells me that the abnormality was first brought to a physician's notice by a father who complained of the smell of his defective children. (The story goes that the physician at first thought the parent suffered from delusions!) The smell is most objectionable. Rarely it is somewhat sweet and rather like bean fields, according to Professor Golla at Bristol. Whether pleasant or not, the smell is highly characteristic. A ward sister told me that she could tell at once by the peculiar smell when one or other of two phenylketonurics passed faeces. A nurse at Calderstones Institution recognised the smell as the same as that of a patient whom she had nursed in another ward more than a year before, a patient whom, unknown to her, I knew to be phenylketonuric. In several institutions incontinent phenylketonurics were bathed thrice daily, or kept isolated on a verandah, because of their objectionable odour. Once recognised, this smell is as easy to detect as is that of acetone in the breath of a diabetic.

The histories of these patients gave no evidence that infective or traumatic agencies might have caused the disorder. The blood Wassermann reaction, obtained in most of the institution cases, was always negative.

No. 2. Propositus 3. Male at age 14.
Note broad shoulders, widely spaced incisor and canine teeth.

On examination, these patients show several unusual features. Their behaviour and mood often differs from that of most low grade defectives. An analysis of the mood of 71 phenylketonurics is given in table III. Nearly a quarter of them are fearful. They are timid, afraid, easily frightened. Such emotion is uncommon among low grade defectives, especially among those in institutional care. The behaviour of these timid phenylketonurics is apparently in harmony with their emotion and consists of a whimpering inactivity. When stimulated they will often run about in an agitated way.

Perusal of Følling's careful records shows that one of his patients was "very frightened", one unduly "shy" (possibly apprehensive), one "moves rather anxiously, often behaves strangely, plucks at her clothes". Another patient had athetoid movements of the arms and fingers, while another maintained a rigid "catatonic" posture, "bending forward with arms bent and fists clenched". Jervis noted movements expressive of fear and anxiety in two of his patients, though most of them were apathetic.

Jervis found "typical athetosic movements of the hands" in several cases, often "combined with movements of a choreiform character". I observed jerky movements at the time of examination in seven of my patients, and inquiry from the nursing staff suggested that the movements occurred in many phenylketonurics. In two cases I was able to photograph the movements. They are confined to the hands and arms. They consist of small rapid pluckings, pointings and fingerings of the face or body. They are jerky, fidgety, irregular in time and in nature.

No. 3. Female sib of Propositus 3 at age 18.
Note distressed expression, fidgety movements of hands.

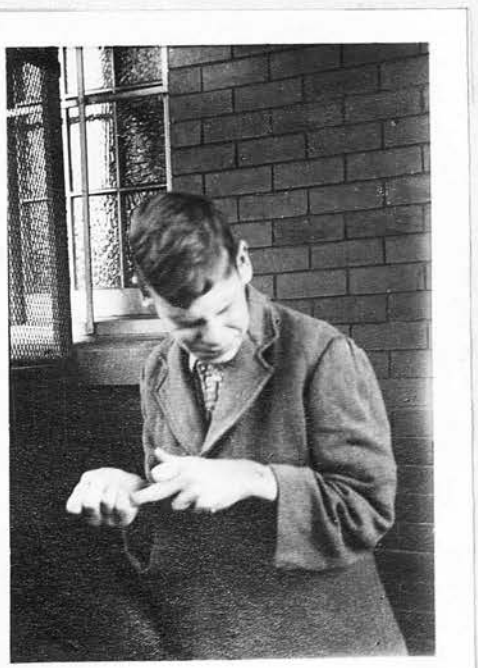
They are sometimes accompanied by facial grimacing (photograph No 6.)or by a distressed expression (photograph No 3.) They never interrupt an intentional movement, they do not show the slow writhing of athetosis nor the quick changes of chorea, and they are not associated with hypotonia. They are more purposive and less involuntary than the movements of true athetosis or chorea. It seems therefore that a distressed emotional state helps to determine their production at least as much as does a possible lesion in the basal ganglia.

Epileptic fits occurred in rather less than half the patients (in 33 out of 77). These fits were apparently quite typical major and minor epileptic convulsions, they occur usually singly, infrequently, and at long intervals of at least several months duration. In 9 cases they occurred only before the age of 2 years. They are not a prominent feature of phenylketonuria, but are certainly more frequent than Jervis has suggested.

The physical examination of these phenylketonurics reveals several abnormalities, none of which, however, occurs in all cases. They often show a general bodily underdevelopment, but in this they do not differ from many other low grade defectives of indeterminate type. Some phenylketonurics are well developed. This is remarkable, as one might suppose that a person who suffered from an inability to metabolise one of the essential amino acids would not grow properly. Følling commented on the broad shoulders and stooping posture of his cases. A kyphosis, sometimes only of slight degree, was present in 29 out of 71 of my patients, and in 19 instances the kyphosis was associated with a remarkably broad chest. A further 5 patients had unusually broad chests.

No. 4. Propositus No. 42 and twin aged 16. Note difficulty in obtaining a motionless photograph, comely facies, flicking movement of hand to mouth.

No. 5. Propositus No. 42. Note good bodily development.



No. 6. Twin, probably monovular, of Propositus 42. Note facial grimace and characteristic fidgety, jerky movements of hands.

Unlike most low grade defectives, phenylketonurics have pleasant and comely facies. Fair hair is characteristic (64 out of 70 cases). In 17 children the hair was strikingly and most unusually fair. Several dark or black- haired parents with other dark haired children commented on the very fair hair of their phenylketonuric child. The colour darkens slightly with age. Blue eyes are usual. In 6 out of 60 cases the irides were pale blue with very little anterior pigment except a slight grey-white mottling.

The teeth show abnormalities. In 23 out of 60 cases the incisor and canine teeth, especially the upper incisors, were separated by gaps, sometimes reaching a millimetre in length. The teeth are sometimes poorly formed and notched, but dentition does not seem to be delayed.

The skin is often pale and delicate in texture, and the cheeks rosy. Both Følling and Jervis have commented on the frequency of skin lesions. Følling noticed white spots and papules in most of his cases, and Jervis found about half of his cases affected with eczema. My patients showed several different skin lesions, freckles, pigment spots, patches of leucoderma, rashes, moles, warts and small papules. Some abnormality of the skin was present in 40 out of 66 cases and 26 patients showed no skin lesions. By far the most frequent skin lesions were small raised pimples up to 2 mm. diameter, usually darker than the skin, often wrinkled, sometimes pedunculated, found on all parts of the body. Sometimes these pimples were larger and had a wart-like structure. They were often associated with multiple dark moles and with small

pigment spots and freckles. A few patients showed small spots of leucoderma. One boy had about 120 moles. Very few patients gave a history of eczema, and fewer still showed any irritative dermatitis. This is in marked contrast to Jervis' findings. Both Jervis and Bates found an undue susceptibility to sunburn. Most of my cases were examined in April and May, before the summer sun was strong, but I have since made enquiries, and I am inclined to think that sunshine does produce a painful erythema in phenylketonurics with undue ease.

Bates, in commenting on the general lack of pigmentation, the ash-blond hair, the pale blue eyes, noted deficient retinal pigment. I have been unable to confirm this. The detection of slight variations in the normal pigmentation of the retina is, however, a matter for the ophthalmologist.

One male and four females showed signs of hypothyroidism, and two males and three females showed signs of hyperthyroidism. One hyperthyroid female died of a malignant adenoma of the thyroid. Six males had unduly small genitals, sometimes associated with undescended testes, and six females, some of whom were hypothyroid, had deficient menses. Følling mentions similar findings in four of his ten patients. Gross endocrine disorder is not a feature of this disease.

The clinical signs found by Følling and Jervis in the examination of the nervous system have been mentioned. None of my patients showed signs of extra-pyramidal disease, nor did I find spasticity at all frequent. The most frequent abnormal finding is an exaggerated and prolonged response from the tendon

reflexes, usually with flexor plantar responses. Out of 70 cases the tendon reflexes were greatly increased in 32, increased in 12 and normal in 26. The abdominal reflexes are present. The limbs are often held rather stiffly against passive movement. This gives the appearance of spasticity, but it is probably an expression of the apprehension of these patients, because, after manipulating for a few minutes the limb can usually be moved freely with ease. This applied even to one boy who always walked on his toes, with an apparently spastic gait.

Slight exaggeration of the tendon reflexes without other signs of disorder of the nervous system is not at all uncommon among low grade defectives of indeterminate type. Such may be considered almost the physiological normal for such persons. The exaggeration of the reflexes in phenylketonuria is pathological.

On the other hand nine patients showed signs of pyramidal involvement, and in five instances the disorder was bilateral. Three patients showed a well marked spastic diplegia with muscle wasting, contractures, and extensor plantar responses. One patient had a coarse rotatory tremor of one arm and hand and three other patients showed a generalised fine tremor associated with signs of hyperthyroidism. The senses of pain and touch and coordination were not found disordered in those patients in whom they could be tested. There were no signs of cerebellar involvement.

Multiple small neurofibromata were a striking feature of the male sib in family I, who came to examination post mortem. As far as I am aware, this was the third autopsy which has been held

on a phenylketonuric. Dr R.M.Stewart tells me that the nerves were not involved in his patient, number 5. The nerves were not examined in the case of the female sib in family 19. The median, ulnar and radial nerves of patient number 3 were exposed surgically and found to be smooth and healthy. On the other hand I have since felt small neurofibromata in five out of 58 patients, and felt nodules suggestive of neurofibromata in a further two patients. These small tumours are sometimes easily felt on the great auricular nerves, and if the sterno-mastoid be put on the stretch, the neurofibromata can be seen as small nodules bulging the skin. They are therefore not a "freak" accompaniment to one case, but are a feature of the disease.

It is interesting that phenylketonurics do not seem to get worse as the years pass. Amaurotic idiocy is similar to phenylketonuria in that it is recessively inherited and is associated with a disorder of metabolism. The amaurotic idiot is a healthy child at birth, but takes a catastrophic course downhill to dementia and death. The phenylketonuric is mentally defective from birth, and rarely becomes worse. Some of the severely affected idiots have a frail hold on life, and die young from intercurrent infections or in status epilepticus, which may be a sign of the progression of the disease. Dr Penton at the Oxford City Mental Hospital tells me that patient number 19 has become less coordinate in the movements of the legs in the past year. Patient number 38 shows some signs of intellectual decay over several years. Seven patients in my series were between the ages of 40 and 50 years. Three of them showed signs of premature senility.

Jervis noted undue senility in a few of his patients.

Summary of Clinical Findings.

Persons with phenylketonuria are mentally defective from birth. A history of maternal ill-health during pregnancy is rather frequent, and the child is often weakly, has a ravenous appetite, and shows disorders of digestion. Two thirds are idiots. They are usually broad stocky people, with a bowed posture, comely facies, very fair hair, blue eyes, and widely spaced incisor teeth. The skin is pale and delicate, unduly sensitive to sunburn, and often shows multiple small papillomata, moles, and occasionally pigmented or leucodermal spots. A highly characteristic, objectionable smell can be observed in at least a quarter of them, and small tumours can be seen and felt on the peripheral nerves of a few. Many are timid, apprehensive creatures, and show nervous flickings of the hands akin to chorea. Some show signs of excess or lack of thyroid and incomplete genital development. About half have infrequent epileptic fits. Exaggeration of the tendon reflexes without other signs of involvement of the nervous system is usual. Slight signs of pyramidal involvement are sometimes seen, and occasionallypyramidal spastic diplegia. The symptoms rarely progress, but a premature senility is often seen.

The clinical picture is thus not as definite as those of mongolism or amaurotic idiocy. Phenylketonuria can be diagnosed with certainty only from an examination of the urine. A green colour on adding ferric chloride is characteristic. On the other hand, the picture of a timid, apprehensive, rather bonny idiot with fair hair, blue eyes, rosy cheeks, widely spaced incisor teeth, exaggerated tendon reflexes, a peculiar odour, and small neurofibromata is striking, and prompts a confident diagnosis.

IV. PATHOLOGY

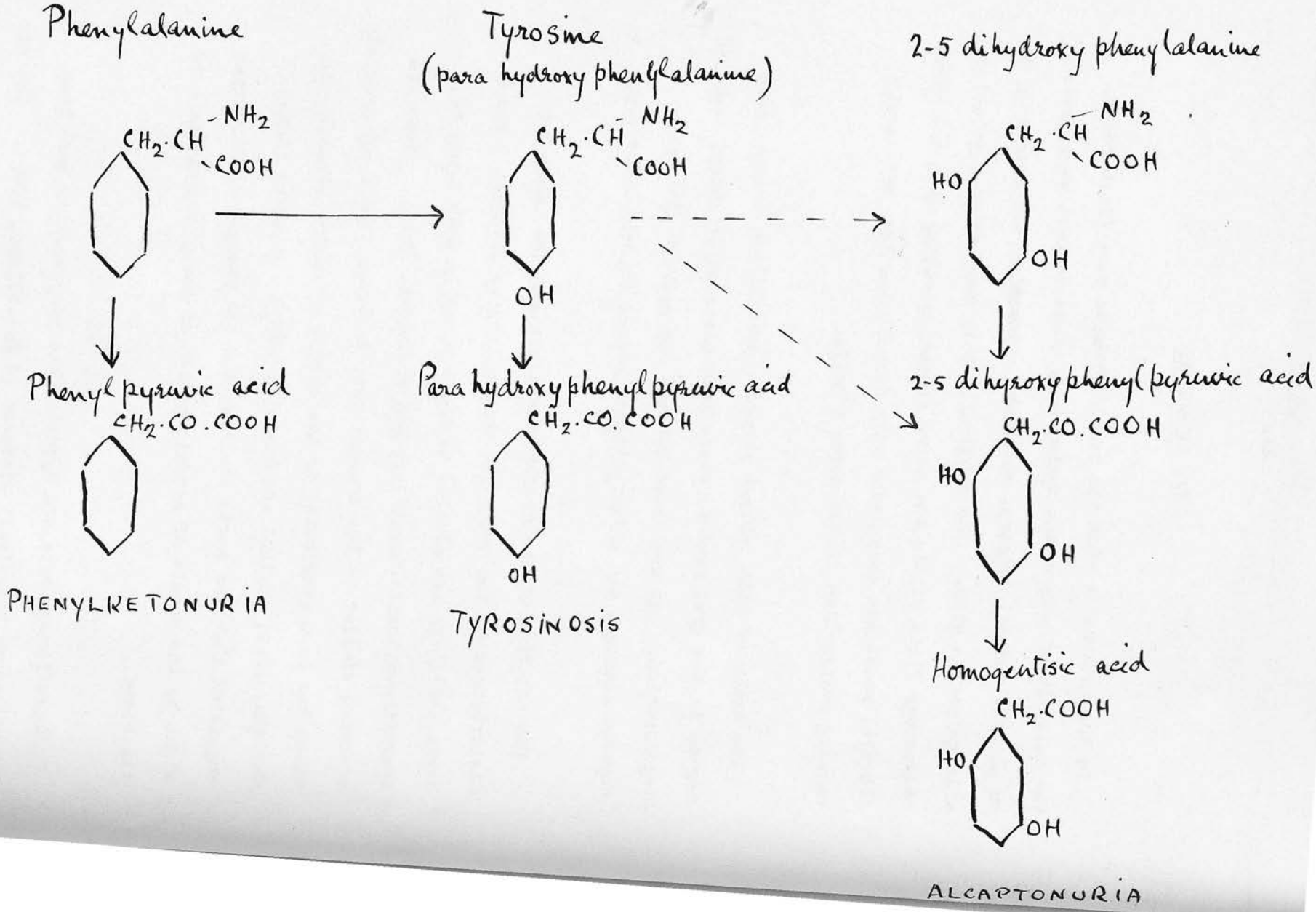
In the patient in whom the neurofibromata were first found, the male sib of propositus number one, these tumours were present on all the nerves, sensory, motor and autonomic, and ranged up to a large pea in size. Histologically they consist of a gelatinous oedematous fluid within the nerve sheath, pressing upon the nerve fibrils, sometimes associated with demyelinization, but rarely causing destruction of the nerve fibrils.

The brain of this patient showed a generalised oedema, more marked in the grey matter, where some nerve cells showed signs of degeneration. As mentioned before, one patient died of a thyroid adenoma, and a few patients showed thyroid disorders.

The relation of the neurofibromatosis and the endocrine disturbances to the metabolic abnormality is obscure. The nerve swellings are similar to those found in some types of neurofibromatosis (Greenfield and Elkington, 1928). They are somewhat similar to the changes seen in hypertrophic poluneuritis which has been attributed to the action of toxins (Russell and Garland, 1930; Hyland and Russell, 1930). Penrose (1939) suggested that the nerve swelling and the changes in the brain might be the result of a toxic action of phenylpyruvic acid in the blood.

Neurofibromatosis and hypertrophic polyneuritis have been described as hereditary diseases (S.A.K.Wilson, 1940). The six examples of Von Reckinghausen's neurofibromatosis in the Royal Eastern Counties' Institution do not excrete phenylpyruvic acid.

Figure I


Phenylalanine
Tyrosine
(para hydroxy phenylalanine)
2-5 dihydroxy phenylalanine
Phenyl pyruvic acid
Para hydroxy phenyl pyruvic acid
2-5 dihydroxy phenyl pyruvic acid
Homogentisic acid
PHENYLKETONURIA
TYROSINOSIS
ALCAPTONURIA

The elucidation of the pathology of phenylketonuria awaits further autopsies, and the experimental feeding of patients and animals with protein substances.

V. BIOCHEMISTRY.

Some of the immediate products of the breakdown of phenylalanine and tyrosine in the body, according to generally accepted views, are illustrated schematically in figure I. Phenylpyruvic acid is a normal breakdown product of phenylalanine and in health is ultimately broken down to carbon dioxide and water. Phenylalanine can be converted into tyrosine, which, when incompletely metabolised, produces the condition known as tyrosinosis. Tyrosine may be converted into a dihydroxy-phenylpyruvic acid, which further breaks down to homogentisic acid, the excretion of which is found in alcaptonuria.

Følling, in his original paper, gave proof of the isolation of phenylpyruvic acid from the urine of phenylketonurics. He showed that the substance contained only carbon, hydrogen and oxygen, determined its empirical formula, and showed that its melting point was not altered by the addition of pure phenylpyruvic acid. He found that the addition of large doses of the amino acid, phenylalanine, to the diet of the patient produced an increased excretion of phenylpyruvic acid. He concluded that the metabolic disorder involved the incomplete oxidation of proteins, that phenylpyruvic acid is not oxydised and is therefore excreted, and that phenylalanine also is probably not utilized.

Penrose and Quastel (1937) confirmed Følling's work, and showed that in phenylketonuria at least half the phenylalanine in the daily diet is incompletely metabolised. They decided that the metabolic disturbance is due largely to a diminished rate of oxidation of the benzene ring in phenylpyruvic acid. They found that feeding with the three forms of phenylalanine, phenylpyruvic acid, but not alanine nor tyrosine, produced an increase of phenylpyruvic acid in the urine. They also showed that normal persons metabolise laevo-phenylalanine more easily than dextro-phenylalanine.

Jervis (1937 and 1938) estimated that on an average diet, phenylketonurics excreted from 0.68 to 2.8 grams of phenylpyruvic acid each day. He did many feeding experiments, and agreed that the disorder was essentially one of failure to oxidize phenylpyruvic acid.

There are as yet only a few more papers on the biochemistry of phenylketonuria.

Følling and Closs (1938a) found traces of laevo-phenylalanine in the blood and urine of normal persons on a mixed diet. An increase of the amino acid in the diet produced a slight increase of the laevo form in the blood and urine. On the other hand, l-phenylalanine could be clearly demonstrated in the blood and urine of patients with phenylketonuria. These workers also thought that the urine of parents of phenylketonurics, though it contained no phenylpyruvic acid, did contain slightly larger amounts of l-phenylalanine than occurred in the urine of control persons. The usual chemical tests were not sensitive enough to detect small quantities of the amino acid. The test used in these experiments

was divised by Closs and Henrikson, 1938, and depended on the fact that bacillus Proteus will break down l-phenylalanine to phenylpyruvic acid.

The work of Peters and other members of the Oxford School showed that the metabolism of pyruvic acid in the brain depends on the presence of a sufficient quantity of vitamin B1. Following this up, Closs and Følling (1938b) showed that white rats on a diet deficient in vitamin B1 excreted phenylpyruvic acid, especially when l-phenylalanine was added to the diet. They decided, however, that this phenomenon did not throw much light on the nature of phenylketonuria. They also observed (Følling and Closs 1938c) that when the rats were fed with l-phenylalanine in an equal quantity of sodium hydroxide, alcaptonuria was produced, and homogentisic acid could be clearly demonstrated in the urine. They further showed (Følling and Closs 1938d) that phenylketonurics excreted phenyllactic acid, which probably arose from phenylpyruvic acid in the organism.

In a short paper Rhein and Stoeber found that phenylpyruvic acid in the urine of patients with Følling's syndrome was best preserved by adjusting the reaction to pH 4 and adding chloroform.

In an interesting recent paper, Levine, Marples and Gordon found that premature infants fed on cows' milk (which is rich in phenylalanine and tyrosine) excreted a hydroxyphenyllactic acid. They suggested that this metabolic aberration in infants is an interrelated function of the level of intake of phenylalanine and tyrosine, and the degree of saturation of the tissues with vitamin C. They thought that the intermediary metabolism of these amino acids could be usefully studied in these infants.

My colleague, Dr Robert Cook, has been studying the biochemistry of phenylketonuria. It seems that it is complicated and that phenylpyruvic acid is not the only abnormal substance excreted by these persons, but our joint experiments are outside the scope of this thesis.

The discovery that an anomaly of protein metabolism is associated with gross mental changes naturally prompts a search for metabolic disorders in other mental defectives and in the insanities. Quastel and Wales (1938) found that a group of 18 patients with catatonic schizophrenia had a diminished ability to excrete hippuric acid. Their findings were criticised by Strøm -Olsen and Greville (1938) on the grounds that their results might be produced by slow absorption from the gut in these stuperose patients. Quastel and Wales eliminated this possibility by feeding the drug intravenously, and still found a faulty detoxication in catatonics. I am not convinced that their patients were all examples of catatonic schizophrenia, but this is of secondary importance. It would be remarkable if such a disorder could be proved to exist in any group of psychotic persons.

VI. GENETICS

The rediscovery of Mendelism (1865) by Bateson (1909) has in this century led to a great increase in our knowledge of inheritance, particularly from the work of the American school on the fruit-fly, under T.H.Morgan (1932), and in this country from the theoretical studies of Fisher (1930), Haldane (1932), Hogben (1931) and Penrose (1934). Our knowledge of human heredity has been summarised by Gates (1929), Cockayne (1933), Blacker (1934), and by Penrose on mental deficiency (1938).

The Mendelian laws of inheritance are laws of probability, and their proof involves the application of statistical technique. In the case of a few diseases, unshakable proof of inheritance and of its mechanism can be gained from a simple statistical analysis of an adequate amount of material, but in many diseases the elucidation of the relative effects of heredity and of environment, and proof of inheritance, may involve mathematical technique of great complexity.

Diseases which in medicine are spoken of as hereditary are usually examples of Mendelian dominance, and indeed incomplete dominance is probably the most frequent type of inheritance in man, ~~Levit~~ ( ). A disease determined by a single dominant genetic factor is transmitted down the generations from one parent to about half the children. Huntington's chorea is the classical example.

Diseases inherited as recessive characters are often spoken of as familial diseases. They show a familial incidence among the brothers and sisters, and the parents and other members of the family are usually unaffected.

A disease determined by a recessive factor appears only in a person who receives the abnormal gene from both parents, and therefore carries the gene in duplex form. The parents usually carry only one recessive gene latent in their constitution, and so do not suffer from the disease. As the chances are even that each parent may or may not pass the gene to a child, according to the laws of probability, on the average, one quarter of the children will receive the abnormal gene from both parents and so manifest the disease, one half will receive only one gene, and so will become carriers, and one quarter will be free of any taint.

If a recessive disease is rare in the general population, the carriers of the gene will also be uncommon, and thus a carrier will be more likely to meet another carrier among the mambers of his own family than if he marries at random. Garrod (1909) was the first to give the true explanation of the relationship of consanguineous parentage to the incidence of a rare hereditary disease. A high incidence of consanguitinty among the parents of many examples of a rare constitutional disease is pathognomonic of recessive inheritance (Munro, 1937, 1938)

The tests for recessivity are three. The parents of the affected person are usually unaffected and, in the case of a rare recessive character, they are often consanguineous. The disease has a familial incidence approaching one quarter among the brothers and sisters.

My material on phenylketonuria consists of 47 sibships. Five out of the 47 marriages of the parents of these children were consanguineous, which suggests a parental consanguinity rate of

TABLE IV

Analysis of Sibships by Weinberg "brother and sister" method: all sibs included except miscarriages, stillbirths and died in infancy cause unknown.

No.	S.	t.	t(S-1).	t(t-1).	No.	S.	t.	t(S-1).	t(t-1).
1	8	2	14	2	24	1	1	0	0
2	6	2	10	2	25	1	1	0	0
2a	5	2	8	2	26	10	2	18	2
3	8	3	21	6	27	2	1	1	0
4	5	3	12	6	28	1	1	0	0
5	7	1	6	0	29	2	1	1	0
6	5	1	5	0	30	11	2	20	2
7	2	1	1	0	31	5	1	4	0
8	1	1	0	0	32	5	3	12	6
9	3	1	2	0	33	3	2	4	2
10	6	2	10	2	34	3	2	4	2
11	5	2	8	2	35	3	2	4	2
12	3	1	2	0	36	9	2	16	2
13	2	1	1	0	37	3	2	4	2
14	6	2	10	2	38	1	1	0	0
15	1	1	0	0	39	12	3	33	6
16	5	1	4	0	40	7	3	18	6
17	4	1	3	0	41	8	3	21	6
18	13	4	48	12	42	2	1	1	0
19	4	3	9	6	43	10	3	27	6
20	4	1	3	0	44	4	2	4	2
21	4	1	3	0	45	2	1	1	0
22	6	2	10	2	46	6	4	20	12
23	2	2	2	2					

S = number in sibship. t = number phenylketonuricin sibs

$$\text{Ratio} = \frac{\text{phenylketonuric}}{\text{normal}} = R = \frac{t(t-1).\ 100}{t(S-1)} = 25.7$$

$$\text{Standard error} = \sqrt{\frac{R(100-R)}{\Sigma\ S}} = 2.9$$

In tables IV and V the phenylketonuric monovular twins have been counted as one case

somewhere about ten percent. The normal rate of cousin marriage in the general population is about one per cent. The difference in the case of phenylketonuria is certainly significant, and points strongly to recessivity.

The theorem of the relationship of parental consanguinity to the incidence of constitutional disease depends on the concept of gene frequency in the population, and has been elaborated by Lenz (1919) and Dahlberg (1929). According to a formula first described by Lenz, the incidence of consanguineous unions among the parents of affected persons can be estimated from the incidence of the disease in the general population. The incidence of consanguineous marriages is approximately $\frac{a}{a - 16p}$, When a is the incidence of cousin marriages in the general population and p is the frequency of the rare recessive gene. The frequency of the gene is measured by the square root of the incidence of the disease in the general population.
If a is 0.008 and p is 0.004 (corresponding to the lower limit of the incidence of phenylketonuria, 2 per hundred housand) then, by the formula, the incidence of parental consanguinity in phenylketonuria is about ten per cent, which accords well with the observed facts. An incidence of phenylketonuria of 4 per hundred thousand corresponds, by the formula, to a consanguinity rate of 7%, and an incidence of 8 per hundred thousand to a rate of 5%. Jervis found 5% parental consanguinity (7 cousin marriages in 125 families) in his material.

None of the 94 parents in my material were mentally defective and the urines of 45 parents who could be examined contained no phenylpyruvic acid. The disease therefore does not usually occur in the parents.

TABLE V.

Factorial Analysis of the Sibships.

Size of Sibship. S.	No. of Sibship. N_S	No. of Sibs. $S.N_S$	No. of Sibs Phenylketonuric.	Expected No. $\frac{S.N_S}{4} \cdot \frac{1}{1-(\frac{3}{4})}$	Variance $N_S \cdot KS$
1.	6	6	6	6.00	0.000
2.	7	14	8	8.00	0.857
3.	6	18	10	7.78	1.578
4.	5	20	8	7.31	2.101
5.	7	35	13	11.47	4.143
6.	5	30	12	9.12	3.880
7.	2	14	4	4.04	1.940
8.	3	24	8	6.67	3.516
9.	1	9	2	2.43	1.380
10.	2	20	5	5.30	3.182
11.	1	11	2	2.87	1.805
12.	1	12	3	3.10	2.020
13.	1	13	4	3.33	2.233
Total	47	226	85	77.42	28.64

The difference between the observed and expected values here is 7.58, which is little greater than the standard error, $\sqrt{28.64}$, or 5.35. Observation and expectation are in accord.

My 47 sibships contained 73 undoubted cases of phenylketonuria and a further 12 mentally defective children, who died before examination, but who probably were also affected. The urine of 54 normal healthy sibs, who could be examined, contained no trace of phenylpyruvic acid. A disease in which affected persons can be sharply differentiated from unaffected persons by a chemical test is peculiarly suitable for genetic study. There is no dubiety about those who are affected and those who are not. It will be observed that phenylketonuria segregates sharply in the sibships, a point in favour of determination by a single Mendelian factor.

The crude incidence of phenylketonuria in the sibships has little value for genetic analysis. 85 cases of phenylketonuria among 261 sibs gives an incidence of 33 per cent, which is greatly in excess of the theoretical expectation of 25 per cent affected. One difficulty in the genetic analysis of a recessively determined disease is that since human families are small (and average about four children per family) many parents who carry the gene will by chance have no affected offspring, and so will be left out of any survey of the disease. Thus for every family of a single and affected child, there would be three families of single children who are unaffected. One method of removing this difficulty is to assume that the families of affected and unaffected persons have a binomial distribution.

According to Weinberg's brother and sister method of analysis, Weinberg (1925), the incidence of phenylketonuria in the sibships is 25.7 per cent, with a standard error of 2.9 (see table IV).

TABLE VI

Sex and Clinical State of Members of 47 Sibships.

	Phenyl-ketonuric.	Normal.	Died under 5 years old.	Total.
Male.	37	60	23 (1)	120
Female.	43	68	20 (2)	131
All cases.	80	128	53	261

(1) includes 2 probable phenylketonurics

(2) " 4 " "

This accords well with the theoretical expectation of 25 per cent on the hypothesis of determination by a single recessive gene . Using Hogben's more accuate method of factorial analysis (see table V), the difference between the observed number of sibs affected and the number expected to be affected on the hypothesis of determination by a single recessive gene is 7.6 with a standard error of 5.4. Observation and expectation again agree. The tests for recessive inheritance are fulfilled and we can say with confidence that phenylketonuria is determined by a single ~~re~~ recessive Mendelian factor. Confirmatory evidence comes from the analysis of the incidence of the disease among other relatives. The incidence of phenylketonuria is nil in 23 half-sibs, nil in 62 grandparents, two cases in 416 uncles and aunts, and two cases in 571 first cousins. These four cases of phenylketonuria among distant relatives occurred in two sibships, and in both these sibships the parents were consanguineous.

VII. FURTHER ANALYSIS OF THE FAMILIES.

The incidence of phenylketonuria among all relatives has already been mentioned. Other mental disorders occurred in the families. Many other infective and constitutional bodily diseases were found, such as gastric disorders, duodenal ulcer, nephritis, arteriosclerosis and tuberculosis. Of such bodily diseases, only endocrine disorders will be analysed here.

Propositi and Sibs.

The 47 phenylketonuric propositi consist of 21 males (one feeble-minded, 6 imbeciles, and 14 idiots) and 26 females (one feeble minded, 9 imbeciles and 16 idiots). All members of the 47 sibships are recorded in table VI, and the sibs alone in table VII. The ratio

Table VII.

Sex, Mental Grade and Clinical State of Sibs in 47 Sibships.

	Mental Grade.							Died under 5 Years.					
	Not Phenylketonuric				Phenylketonuric			Prob. Phenyl-ketonuric	Prob. Normal	State Unknown	Still Born	Mis-Carry	Total
	S	A	D	FM	FM	Imb	Idiot						
Male	8	49	2	1	2	8	6(1)	2	8	5	6	2	99
Female	4	60	3	1	2	5	10(2)	4	5	8	3	0	105
Sex unknown												10	10
All cases	12	109	5	2	4	13	16	6	13	13	9	12	214

(1) Includes one died over 5 years probable phenylketonuric.

(2) - 5 - - - - - -

of phenylketonuric to normal members in the sibships differs little in the two sexes. In table VII mental grade is recorded as Superior, Average, Dull, Feeble-minded, Imbecile and Idiot. There are two feeble-minded sibs who are **not** instances of phenylketonuria. This incidence of mental defect, 2 in 214, is about that in the general population.

The age distribution of the propositi and sibs is given in table VIII. It will be seen that of the sibs who were not phenylketonuric, only five males and eight females exceeded 45 years of age. No less than seven of these thirteen sibs suffered from psychosis. These psychoses occurred in three families. Two females in family number 2a had depressive psychosis beginning at ages 48 and 54. In family number 5 two females had depressive psychoses beginning at ages 45 and 50, one male became psychotic in the late forties and took his life, and another male had an intermittent psychosis from 28, worse after 50 when he had persecutory ideas. In family number 6 one female had acute depressions at 33 and at 45. There were no other mwntal abnormalities in the sibs except the two instances of feeble-mindedness already noted.

As regards bodily diseases among the sibs, one female had exophthalmic goitre at age 35, cured by surgery. One boy in family number 11 was probably a case of diabetes insipidus. Professor D.M.Dunlop kindly arranged to take this boy into the Royal Infirmary of Edinburgh for investigation, but the boy died of appendicitis. Two other sibs were tiny people, but showed no obvious sign of diabetes insipidus.

TABLE VIII

Age Distribution of Propositi and of Affected and Unaffected Sibs.

Age in Years.	SIBS Alive				SIBS Dead				PROPOSITI	
	Not phenyl-ketonuric		Phenyl-ketonuric		Not phenyl-ketonuric		Phenyl-ketonuric		Phenyl-ketonuric	
	M	F	M	F	M	F	M	F	M	F
0-4	3	4	1		13	13	2	3		1
5-9	3	3	1	1			1	2	1	2
10-14	5	4	2	2	1			1	5	4
15-19	10	11	5	2	1		1	2	6	3
20-24	6	7	2	2	2	1		1	3	4
25-29	8	9	1	1				1	2	2
30-34	5	7	1	1		2			1	3
35-39	10	8							1	3
40-44	1	3	1	1		1				2
45-49		4			1				1	
50-54	1			1		2			1	1
55-59										
60-64					1	2				
65-69										1
70-74					1					
75-79										
80-84	1									
Mean Age.(1)	26.6	27.1	20.6	24.3	36.8	45.0	12.5	16.1	22.3	27.1
Number over 5 Years	50	56	13	11	7	8	2	7	21	25

21 stillbirths and miscarriages are excluded.

(1) Excluding those under five years.

I have been fortunate in being able to compare my phenylketonuric material with a series of families of mental defectives who were not phenylketonuric collected by Penrose at Colchester. I have extracted from the material published in his survey, Penrose 1938 a, the records of 653 families of patients of imbecile and idiot grade, and compared the incidence of mental defect and of psychosis in my families with those in this control material. The sibs in these two groups of families are analysed in table XII. The observed number of imbeciles and idiots in my material greatly exceeds expectation and is, of course, caused by the familial incidence of phenylketonuria. Sibs of superior mental grade are six times in excess of expectation. This greater segregation of intelligence could be taken as evidence of the action of single genetical factors determining intelligence in these families.

The incidence of psychosis in families, unlike that of mental defect, varies with the age of the members. The older the relatives the greater the chance that they have, or have had, a psychosis. The mean age of the phenylketonuric propositi is 23.6 years, and that of the 653 control patients is 24.0 years. As the control patients are slightly the older, one may expect their parents and other relatives also to be slightly older than the relatives in my families. But the difference in age in the two groups of patients is small, and only a slightly greater incidence of psychosis in the control families can be expected on this account. The indidence of psychosis in the phenylketonuric families is more than twice expectation, but is barely statistically significant.

TABLE IX

Age Distribution of Parents

Age in Years.	Father		Mother		Total.
	Alive	Dead	Alive	Dead	
20-24		1			1
25-29					-
30-34	3	1	3	1	8
35-39	2	2	7	3	14
40-44	6		5	1	12
45-49	5	1	2		8
50-54	2	1	2	1	6
55-59	7	2	9		18
60-64	1		3	2	6
65-69	3	1	1	2	7
70-74	2		1		3
75-79	1	1		2	4
80-84	1	1			2
Mean Age.	52.8	52.0	49.0	54.6	51.5
Total number.	33	11	33	12	89 (1)

(1) Excluding 3 living fathers and 2 living mothers of unknown age.

Half-sibs.

There were only 23 half-sibs, 8 male and 15 female. None are mentally defective. One male is a hypochondriacal epileptic aged 39, who is able to work in the community, and one male had a depressive psychosis from age 44 till his death at 70 years. Only four half-sibs exceeded 40 years of age.

Parents.

None of the 94 parents were mentally defective, and no parent was found to excrete phenylpyruvic acid. Five parents were of superior intelligence, and ten parents were dullards but were able to earn their living. (Table XIII). The mean age of the parents is 51.5 years (tableIX). The mean age of the mothers who are alive is 49.0 years, and there are 15 mothers living between the ages of 30 and 44 years. The sibships are therefore not all complete, but probably not many more children will be born to these mothers.

The incidence of psychosis in the parents is about the same as that in the control families (Table XIII). There are five instances of psychosis and they all began after middle life. Two fathers had paranoid psychoses in the fifties (families nos. 1 and 43), two fathers had depressive psychoses in the forties (families nos. 2 and 23), and one mother had a senile psychosis (family 2a). Forty four parents exceeded 45 years of age, and so the incidence of psychosis in parents who reached middle age is about one in nine.(5 in 44).

TABLE X

Age Distribution of 143 Grandparents

Age in Years.	Male		Female		
	Alive	Dead	Alive	Dead	Total
30-34		1			1
35-39		1		1	2
40-44		2		3	5
45-49		4		5	9
50-54		4		7	11
55-59	1	3	4	3	11
60-64	4	6	6	6	22
65-69	6	7	1	7	21
70-74	5	6	5	5	21
75-79	4	2	6	5	17
80-84	2	9	3	5	19
85-89	1	1		1	3
90-94					
95-99					
100-104				1	1
Mean Age.	71.2	65.1	69.9	64.1	66.6
Total Number.	23	46	25	49	143

Three fathers and two mothers had anxiety states and three fathers were psychopaths. This incidence of " neurosis " is rather higher than that in the control families. One mother died at 60 years of hyperthyroidism (family 24).

Grandparents.

The mental state of 152 of the 188 grandparents was known. No grandparent was mentally defective. Seven male and six female grandparents were psychotic, and one female had a mental disorder of unknown type. Two males and one female had neuroses. Two males had depressions in the fifties, one died in an epileptic psychosis at 64, one died with paranoid delusions at 83, one died insane at 59, one died insane at 37, and another psychotic died over 70 years. Two females were alive in the seventies and were hypomanic, two in the seventies had unknown psychoses, and two had senile psychoses. One male was a psychopath, and another hypochondriacal. One female had a chronic anxiety state. The age of 143 grandparents was known and is recorded in table X. A further 6 males and 3 females died over 70 years. In all, 144 grandparents exceeded 45 years of age, and the incidence of psychosis among them is one in twelve. Some parents married their cousins, and in this way six grandparents were consanguineous. The incidence of mental disorder among these grandparents was much higher. Two were psychotic and one had a chronic anxiety state.

Uncles and Aunts.

Five uncles and aunts were mentally defective (Table XIV). Two of these were idiots who died in infancy and were probably phenylketonuric. There were, in all, 486 uncles and aunts.

TABLE XI

Age Distribution of Uncles and Aunts

Age in Years.	Male	Female	Sex Unknown	Total
15-19	5	3		8
20-24	11	3		14
25-29	13	7		20
30-34	12	10		22
35-39	17	12		29
40-44	25	13		38
45-49	12	22		34
50-54	20	21		41
55-59	9	16		25
60-64	14	13		27
65-69	10	6		16
70-74	1	5		6
75-79		3		3
80-84	1			1
Mean Age	44.2	48.6		46.3
Total Number.	150	134		284
Age unknown	85	48		133
Miscarry & Stillborn.	2		7	9
Died under 5 years.	27	17	16	60
Total.-	264	199	23	486

Table XII.

Mental Grade and Clinical State of Sibs in Phenylketonuric and Control Families.

	Mental Grade										Clinical State	
	S	A	D	FM	Imb	Id.	D.I.	SB	U	Total	Psy.	Neu.
47 Phenylketonuric Families (a)	12	109	5	6	13	22	26	21	0	214	7	0
653 R.E.C.I. Families Expectation on (a)	2	98	10	5	4	2	21	27			2.6	1.
Observed	40	1968	203	109	71	38	418	453	110	4420	52	34

(1) Excluding 6 probable phenylketonurics.

D.I. - died infancy
SB - still births and miscarriages
U - state unknown
Psy - psychoses
Neu - psychoneuroses and psychopathy

Table XIII.

Mental Grade and Clinical State of Parents in Phenylketonuric and Control Families.

	Mental Grade								Clinical State	
	S	A	D	FM	Imb	Id.	U	Total	Psy.	Neu.
47 Phenylketonuric Families (a)	5	73	10	0	0	0	6	94	5	8
653 R.E.C.I. Families Expectation on (a)	0.5	77	9	5	0	0			4.5	4.5
Observed	7	1073	129	67	0	0	2	1306	63	63

The mental state of 391 was known, the others died in infancy or were unknown. Only six of the 391 uncles and aunts were psychotic. Three males had depressive psychosis(families 2,2a and 11), one male had a psychosis of unknown type (family 43), all beginning in middle life. One male was a feeble minded and deteriorated epileptic. One female had a psychosis of organic type in middle life, probably associated with hyperthyroidism (family 11). The exact age of many uncles and aunts was not known. The mean age of the others is 46.3 years (table 11). Approximately 190 uncles and aunts exceeded 45 years of age. The incidence of psychosis with onset in middle life among them is 5 in 190, or about 1 in 40. This is less than the incidence in the control families (table XIV). Six uncles and one aunt suffered from neuroses. Three uncles and one aunt had anxiety states (families 13, 14 and 15), one uncle had an anxious hypochondriasis and possible hyperthyroidism (family 11), one was a psychopath (family 8) and one was a chronic alcoholic (family 4). There were another three instances of hyperthyroidism in family 11.

Nephews and Nieces and First Cousins.

The nephews and nieces and first cousins comprised the following : -

	Adult			Died infancy			Mis-carry.	Total.
	m	f	sex unk.	m	f	sex unk.		
Nephews and nieces	38	38	6	4	2	-	4	92
First cousins	293	264	45	15	9	2	6	634

There were no mental abnormalities among the nephews and nieces. Three first cousins were idiots and one of these was known to be phenylketonuric (family 30). The incidence of

Table XIV.

Mental Grade and Clinical State of Uncles and Aunts in Phenylketonuric and Control Families.

	Mental Grade									Clinical State	
	S & A	D	FM	Imb	Id	DI	SB	U	Total	Psy	Neu
47 Phenylketonuric Families (a)	385	1	2	1	2	58	9	28	486	6	7
653 R.E.C.I. Families Expectation on (a)	375	9	3	1.7	0.8					9	3
Observed	3935	90	34	18	8			1997	5102	95	31

(1) Excluding 2 idiots.

Table XV.

Mental Grade and Clinical State of First Cousins in Phenylketonuric and Control Families.

	Mental Grade									Clinical State	
	S & A	D	FM	Imb	Id	DI	SB	U	Total	Psy	Neu
47 Phenylketonuric Families (a)	572	2	2	1	3	26	6	22	634	0	0
653 R.E.C.I. Families Expectation on (a)	289	11	6	2	0.5			325		3	2
Observed	2444	96	51	19	4			2751	5365	26	17

idiocy is above expectation (table XV). One first cousin was a Mongolian imbecile (family 22), and two others were feeble-minded. There were no psychoses among the first cousins. Their mean age will be about the same as that of the propositi and sibs, and will therefore be in the twenties. Thus they cannot suffer from psychoses of later life.

The relation of mental and endocrine disorders to phenylketonuria.

The hypothesis that the heterozygotes of phenylketonuria tend to suffer from involutional psychoses requires careful investigation. Phenylkatonuria varies much in clinical severity. No doubt this is in part determined by the presence of modifying genetic factors in some families. One may expect the heterozygotes to vary yet more widely. The absence of favourable modifying factors in some persons may permit the expression of the recessive gene in the soma. Environmental factors will also have an effect. For instance, the association of such factors as financial loss and bereavement with the onset of involutional melancholia is well established. The absence of modifying genetic factors and the presence of unfavourable environmental factors may in some families allow the recessive gene to express itself in heterozygous form as a partial dominant. The concentration of psychoses in families 2 and 2a may be an example of this. We may expect, therefore, the incidence of mental disorder to vary in the different relatives according to the proportion of heterozygotes among them. But the incidence will probably also vary in different families with the presence of modifying genetic factors in some and not in others. The incidence will be further influenced in an irregular way by environmental factors.

The effects of these last two influences can be eliminated only by the collection of many families. My families are few, but they have been carefully investigated. Unfortunately, not many relatives of my patients have reached an age when they can suffer from involutional disorder and therefore this material contains only rather meagre facts bearing on this important topic.

The relatives for analysis are the parents, sibs, half-sibs, grandparents and uncles and aunts. There are 33 instances of psychosis among these relatives. These psychoses occur thus. --

Psychosis	male	female	total
Onset in early or late life	5	7	12
Onset in middle life	15	6	21
All psychoses	20	13	33

The psychoses which began in early life comprise three instances of epilepsy, one of paranoid delusions and one of unknown type, all in men. Seven senile psychoses occurred in women. Fourteen of the 21 psychoses which began in middle life were of affective type, three were paranoid with depressive features, one was an undiagnosed organic reaction type and three were of unknown type. The relative proportions of these various psychoses are about those which occur in the general population. The proponderance of affective psychosis is not unusual.

The incidence of psychosis in the various relatives shows little relation to the incidence of heterozygotes (table XVI). The incidence of psychosis in the parents who are all heterozygous, is one in nine, while the incidence in the sibs,

TABLE XVI

Incidence of Heterozygotes and of Psychoses in Specified Relatives.

	Proportion Heterozygous.	Proportion Psychotic.	Number (1) Psychotic.	Number over 45 years.
Parents.	1 in 1.	1 in 9.	5	44
Unaffected Sibs.	2 in 3	1 in 2	7	13
Half sibs.	1 in 2	1 in 4	1	4
Grandparents	1 in 2	1 in 12	12	141
Consanguineous Grandparents.	1 in 1	1 in 3	1	3
Uncles and aunts.	1 in 2	1 in 40	5	190

(1) Age of onset over 45 years.

TABLR XVII

Incidence of Heterozygotes & of All Mental and Endocrine Disorders in Specified Relatives.

	Proportion Heterozygous	Proportion Disordered	Number Disordered	Number of [illegible] Mental Stat
Parents	1 in 1	1 in 6	14	88
Unaffected Sibs.	2 in 3	1 in 14	9	128
Half Sibs.	1 in 2	1 in 10	2	21
Grandparents	1 in 2	1 in 9	17	152
Consanguineous Grandparents.	1 in 1	1 in 2	3	6
Uncles & aunts.	1 in 2	1 in 24	16	389.

(1) Excluding all died under 5 years.

which should be less, is very high, one in two. These psychoses in the sibe are concentrated in three families. Environmental factors were important in precipitating some of them. The incidence of heterozygotes in the half-sibs, grandparents, uncles and aunts is the same, but the incidence of psychosis varies widely. Some, but not much, of this variation may be the result of incomplete ascertainment. If there be a relation between hetero-zygosity and psychosis then many more instances of psychosis should have occurred among the uncles and aunts. On the other hand, psychosis is more frequent among the consanguineous grandparents who are all heterozygous than among other grandparents only half of whom may be expected to carry the gene. My material, therefore, produces only slight evidence that the heterozygotes of phenylketonuria tend to suffer from psychosis. The only striking fact is that seven out of 13 sibs over 45 years of age are insane.

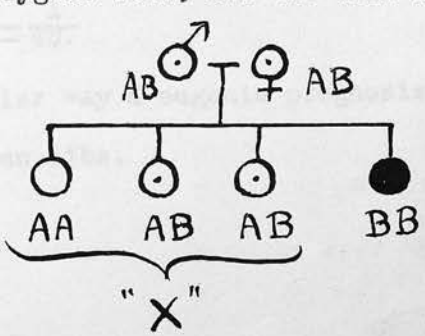
The possible relation of minor mental disorders and of endocrine malfunction to phenylketonuria is suggested by family charts such as no.11 in which several uncles and aunts have mental disease and hyperthyroidism, sometimes associated together. Anxiety states in the parents might have a genetic relation to the apprehensive agitation of the phenylketonuric. Similarly with hyperthyroidism. It may be recalled that one phenylketonuric died of a malignant adenoma of the thyroid. The incidence of all mental and endocrine disorder among the relatives is given in table XVII. The incidence of these disorders taken together does to a slight extent vary with the incidence of heterozygosity, which suggests a relation between the two.

This problem of the relation between the heterozygotes and mental or endocrine disorder can only be solved by the investigation of more families, particularly those containing many relatives who have reached old age. Both Følling and Jervis mention a few instances of psychosis in their families but they did not investigate the family histories fully. Another and indirect approach to the problem is to search for a latent biochemical abnormality in the heterozygotes which might indicate a tendency to mental breakdown. The evidence produced from my family histories warrants further work on the problem.

VIII. Note on Eugenic Prognosis.

As the inheritance of phenylketonuria is now well established, and as its incidence in this country has been estimated, it is possible to determine with a fair degree of accuracy the chances that any member of a family in which a case of phenylketonuria occurs will bear a phenylketonuric child.

The disease is inherited as a single Mendelian recessive character. There is no reason to suppose that the disease does not manifest itself in every person who carries the abnormal gene in homozygous form. In a family of four children born to parents who carry the gene, on the average, one child will carry the gene in homozygous form and have the disease, two will carry the gene in heterozygous form, and one will lack the abnormal gene, thus : -



The chance that X, one of the three unaffected sibs will carry the gene is thus two in three.

From the theory of gene frequency (see discussions by Hogben 1931 and Gates in Blacker 1934), the incidence of the hererozygotes can be determined from the incidence of the homozygotes. If the incidence of the homozygotes (BB) be $\frac{1}{n}$, then the incidence of the heterozygotes is $\frac{2}{\sqrt{n}}$. If the frequency of phenylketonuria be taken as 4 in 100,000, then the frequency of the carriers is 8 in $\sqrt{100,000}$, which is approximately $\frac{8}{300}$. Therefore the chance that X marries a carrier is 8 in 300. The chance, if these chances happen, that a child is affected is one in four.

The total chance that X will bear an affected child is

$$\frac{1}{4} \times \frac{2}{3} \times \frac{8}{300} = \frac{1}{230}$$

Thus about one in 230 of the marriages of sibs of phenylketonurics will produce affected offspring.. If the incidence of phenylketonuria be taken as its lower limit, namely 2 in 100,000, then the chance that X will have an affected child is about one in 450.

The above calculation is based on the assumption that the sib marries at random. If the sib marries a blood relative than the chances of an affected offspring are much increased. For instance, the hereditary likeness between first cousins is one eighth. If X marries a first cousin the chance that X has an affected child is $\frac{1}{4} \times \frac{2}{3} \times \frac{1}{8} = \frac{1}{48}$.

In a similar way a eugenic prognosis can be estimated for other relatives than sibs.

The chance that the parents of an affected child will have another affected child is one in four. It seems right and kind that parents should be warned of this danger, so that they may plan their lives accordingly. I think that these parents should be given this advice whether or not they ask for it. If the sib of a phenylketonuric asks for advice about having children, he or she may be told that, in marriage with a first cousin, the risk of an affected child is about one in fifty, but in marriage outside the family the risk is much less, being only about one in 200 or less.

There are many grave social objections to compulsory sterilization or control of marriage. Even if such measures were put into force they would have little effect on the incidence of recessively determined diseases such as phenylketonuria. The vast majority of phenylketonurics do not have children. None of my patients married or produced children. Although all the children of a phenylketonuric woman will be carriers, she cannot produce an affected child unless she mates with a carrier. (Jervis mentions one phenylketonuric woman, who had four children, two affected and two normal. She must have mated with a carrier.) Supervision of mental defectives in the community or their segregation in Institutions will prevent these happenings.

Since the incidence of consanguineous parentage in phenylketonuria is about ten per cent, the prohibition of all cousin marriage would decrease the incidence of the disease in the next generation by only ten per cent.

Sterilisation of one or other parent of an affected child would have greater effect. In cases such as this, voluntary sterilization

would be useful, but the parents can always take other precautions to avoid a repetition of their tragedy.

In the case of the healthy sibs of an affected person, the limitation, whether by compulsory or voluntary means, of the families of large numbers of socially valuable persons, a third of whom do not carry the gene at all, would be quite incommensurate with the results obtained. I therefore disagree with Kallmann (1938) who advocates widespread limitation of families in schizophrenia, another disease in which recessive genetical factors play a part.

Some of the carriers in phenylketonuria may possibly develop insanity in middle life, but environmental factors must also help to produce such disease, and such factors may be avoided or controlled. The possibility of such insanity is not sufficient reason for preventing all possible carriers from leading healthy lives.

It is possible to look forward to a time when the carriers of the gene for phenylketonuria may be detected by chemical test. The situation will then be changed. Such carriers may be warned against mating with another carrier, and mental hygiene, and possibly drugs may guard the involutional period of their lives.

Cousin marriage has decreased in Europe in recent generations of humanity. Haldane (1939) has recently pointed out that this has resulted in a rapid decrease in the frequency of clinically severe recessive conditions, followed by a slow increase in the frequency of the genes responsible for them. The frequency of recessive conditions will rise slowly to its old level , but the half completion of this process will require at least 2000 years.

IX. SUMMARY.

This thesis contains a clinical and genetic analysis of 43 British families, in which there were 86 cases of phenylketonuria. The disease is rare. Among more than 4000 mental defectives examined in Institutions, it occurs in about one in a hundred low grade patients, and in about six in ten thousand high grade patients. In the general population the incidence lies between two and six per hundred thousand. There are probably about 1600 cases of the disease in Britain and it is possibly more frequent in the West Country, in Lancashire and in the North of Scotland. No instance has yet been recorded in a Jew.

The metabolic disorder probably involves the incomplete metabolism of phenylalanine and shows itself in the excretion in the urine of phenylpyruvic acid, which is easily detected. The metabolic anomaly is always associated with mental deficiency. Phenylketonuria has not a well defined clinical picture in all cases, and can be diagnosed with certainty only from an examination of the urine. Two thirds are idiots. Many show comely facies, fair hair, blue eyes, wide spaced incisor teeth, delicate skin, sensitive to sunburn and subject to multiple papillomata, a broad and kyphotic chest, and exaggeration of the tendon reflexes. Many are timid apprehensive creatures and show nervous flickings of the hands akin to chorea. About half have infrequent epileptic fits; at least a quarter emit a highly characteristic odour, and small multiple neurofibromata can be felt in a few. The mental deficiency is present from birth; the symptoms rarely progress, but a premature senility is often seen. This clinical account differs much from those previously published.

More than 1500 relatives were recorded. Analysis of the families shows that the rate of parental consanguinity is greatly increased, the parents are unaffected, and the disease has a familial incidence in the sibs. Factorial analysis confirms that the disease is without doubt inherited as a single Mendelian recessive character.

The incidence of psychoses, psychoneuroses, and psychopathies in the various relatives suggests that these disorders may occur particularly among persons who are the carriers of the abnormal genetic factor.

A note on eugenic prognosis is added, and the chances that a healthy sib of a phenylketonuric will have an affected child is estimated.

The literature is reviewed.

SHORT SUMMARY

This thesis analyses 43 families with 86 cases of phenylketonuria, a rare metabolic disorder always associated with mental defect and occurring in about 4 per 100,000 persons, defines the symptomatology, discusses the pathology and biochemistry, proves the inheritance of the disease as a Mendelian recessive character, records the presence of other mental disorders in the families and reviews the literature.

Thomas A. Munro.

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APPENDIX 1.

RECORD OF PARENTS AND SIBSHIPS.

Giving order of birth, age, blood group, urine examination, mental grade, mental and physical state.

KEY TO APPENDIX 1.

1. The sibs are given in order of birth: 'm' denotes male, 'f' female.

2. The propositus in each family is marked by a cross, 'x'.

3. Age is given in years. A plus sign placed after the figure for age indicates death: thus 70 + 3 denotes death at age 70, three years ago. Twins are bracketed together.

4. Blood groups are given according to the ABO and MN series.

5. Urine - p = phenylketonuria: n = not phenylketonuria.

6. Mental grade - Superior; Average; Dull; Feeble-minded; Imbecile; Idiot.

7. Some of the families are interrelated: the relationship is specified in the appendix.

8. Parental consanguinity is denoted by a suffix '*' attached to the father concerned.

Family No. 2 Father's mother sib to mother's father.

2a Father's mother sib to mother's father.

11 Father's mother's mother sib to mother's mother.

20 Father's father sib to mother's mother.

21 Father's mother's father is the mother's father's father.

(In family No. 14 the parents of the father's father were first cousins.

In family No. 25 the mother's parents are 1½ cousins.)

ly er	Relative		Age	Blood group	Urine	Mental Grade	Mental and Physical State
1.	Father.		66	A M 1	n	A	Paranoid delusions since 60.
	Mother.		57	OMN	n	A	Normal: gastritis.
	Sibs.	f. $\frac{10}{12}$ +	?	-	-	-	Unknown, died - fits.
		m.	38			A	Normal.
		f.	36	A M 1	-	A	Normal.
		- - +	?	-	-	-	Miscarriage at 10 weeks.
		m.	29			S	Normal.
		m.	27	A MN 1		A	Normal.
	x	m.	24	A MN 1	p	Idiot	I.Q.2.
		m.	21		n	D	Poor sight.
		f.	19	A MN 1	n	A	Normal.
		m.	$\frac{2}{12}$ + $\frac{4}{12}$	A MN 1	p	Idiot	I.Q. under 10: epileptic.
2.	Father.*		70 + 3	-	n	A	Melancholia, onset 44: nephritis: died cerebral haem.
	Mother.		70	OMN	n	A	Normal.
	Sibs.	x f.	44	OMN	p	Imb.	I.Q.28.
		f.	41	OMN		A	Normal.
		f. 15 +	24	-	-	Idiot	I.Q. below 20: probable phenylketonuric.
		m.	35			A	Normal.
		m.) $\frac{2}{52}$ +	33	-	-	-	Unknown, died - fits.
		f.)	33	OM	n	A	Normal.
		f.	29	A MN 1	n	A	Normal.
2a	Father.*	81 +	14	-	-	A	Normal.
	Mother.	77 +	20	-	-	A	Senile psychosis from 75.
	Sibs.	f.62 +	0	-	n	A	Depressive psychosis since 48.
		x f. 4 +	57	-	-	Idiot	Probable phenylketonuric.
		f.54 +	6	-	-	A	Depressive psychosis at 54: suicide.

≠ Propositus is maternal half-sib of father of family No. 2.

d.)	Sibs.	f.	4 + ?	-	-	Idiot	Probable phenylketonuric.
		f.	44 + 10	-	-	A	Normal: died - peritonitis.
3.	Father.		56	OM	n	A	Normal.
	Mother.		55	A MN 1	n	D	Normal.
	Sibs.	m.	$\frac{2}{365}$ + 28	-	-	-	Unknown.
		m.	27	A M 2		A	Normal.
		m.	25	A M 2	n	A	Normal.
		m.	23	A MN 2	p	Imb.	I.Q.40.
		f.	20	A MN 2	p	Idiot	I.Q.20.
		m.	18	A MN 2	n	A	Tiny.
		x m.	16	A M 2	p	Idiot	I.Q. under 20.
		f.	15	A MN 2	n	D	Tiny.
		f.	11	A MN 1	n	A	Normal.
4	Father.		48 + 21	-	-	S	Psychopath: d. - syphilis of brain ? gumma.
	Mother.		54	OM	n	A	Normal. Gastric ulcer.
	Sibs.	x m.	53	BMN	p	Idiot	I.Q. under 10.
		m.	$\frac{1}{12}$ + 32	-	-		Probable phenylketonuric idiot.
		m.	31	-	-	A	Normal.
		f.	29	A M 2	p	Idiot	I.Q. under 10.
		f.	27	A M 2	n	A	Normal.
5	Father.		77 + 29	-	-	S	Normal.
	Mother.		77 + 33	-	-	A	Normal.
	Sibs.	f.	63 + 25	-	-	A	Unduly melancholy after 50.
		m.	74 + 10	-	-	A	Normal.
		m.	82	-	-	A	Normal.
		m.	48 + 30	-	-	S	Suicide in depression at 48.
		m.	64 + 13	-	-	A	Persecutory delusions from 28 with depression since 50.
		x f.	67 + 2	-	p	Idiot	I.Q. under 10: hyperthyroid: d. thyroid cancer.
		f.	50 + 15	-	-	A	Depression from 45: suicide.

Father.		65 + 6	-	-	A	Normal: d. heart disease.
Mother.		50 + 21	-	-	A	Normal: d. influenza.
Sibs.	f.	23 +(29)	-	-	A	Normal: died in childbirth.
	x f.	51	OMN	p	Idiot	I.Q. below 10: epileptic.
	f.	48	OMN	n	A	Normal.
	f.	45	OM	n	A	Psychotic depression for year at 33: mild depression at 45: now well.
	m.	22 + 21	-	-	A	Normal. Killed in war.
	f.	0 + ?	-	-	-	Stillborn.
Parents.		x -	-	-	-	Unknown.
Sibs.	x f.	41	BM	p	Imb.	I.Q.41.
	f.	36	A MN 1	n	Fm.	I.Q. about 70.
Father		(21)+ 35	-	-	A	Normal (Alcoholic).
Mother		57	-	-	A	Normal.
Sibs	x f.	36	A M 2	p	Idiot	I.Q.26.
Father.		32	OMN	n	A	Normal.
Mother.		31	A MN 2	n	A	Normal.
Sibs.	x f.	9	OM	p	Idiot	I.Q.2.
	- -	+ 6	-	-	-	Miscarriage at 8 weeks.
	m	4	ON	n	A	Normal.
	f	2	A MN 2	n	A	Normal.
Father.		71	-	-	A	Normal.
Mother.		66	-	-	A	Normal.
Sibs.	f.	40	-	-	A	Normal.
	f.	39	-	-	A	Normal.
	m.	36	-	-	A	Normal.
	f.	15 + 20	-	-	Idiot	Probable phenylketonuric.
	f.	33	-	-	A	Normal.
	x f.	30	A BMN 1	p	Idiot	I.Q.10.

Father.*		58	OMN	n	A	Chronic anxiety state.
Mother.		36 + 12	-	-	A	Normal: d. rheumatic heart.
Sibs.	f.	24	OM	n	A	Normal.
	m.	21	OMN	-	A	Normal.
	m.	4 + 14	-	-	Imb.	Probable phenylketonuric.
	x f.	15	OMN	p	Idiot	I.Q.2.: epileptic.
	m	10 + 2	-	n	A	Tiny: ? diabetes insipidus: d. appendicitis.
Father.		59	-	-	S	Normal: prostate removed at 52.
Mother.		55	-	-	A	Normal.
Sibs.	f.	25	-	-	S	Normal.
	m.	20	-	-	A	Normal.
	x f.	16	A MN 1	p	Idiot	I.Q.10.
Father.		33	A MN 2	n	D	Normal.
Mother.		32	A N 2	n	D	Anxiety neurosis since 21.
Sibs.	x f.	11	ON	p	Imb.	I.Q.28.
	- -	+ 7	-	-	-	Mother induced abortion at 3 mths.
	- -	+ 5	-	-	-	Mother induced abortion at 4 mths.
	m	2	A MN 2	n	A	Normal.
Father.		45	A M 2	n	A	Normal.
Mother.		39	ON	n	A	Anxiety state for some years from 35: now normal.
Sibs.	m.	17	A MN 2	-	S	Normal.
	m.	15	OMN	n	A	Normal.
	x m.	13 + 1	-	p	Idiot	I.Q.9.
	m.	10	A MN 2	n	A	Normal.
	m.	5	OMN	p	Imb.	I.Q. about 40.
	f.	$\frac{3}{52}$	OMN		-	Appears normal.

Father.		-	-	-	U	Unknown.
Mother.		38	OM	-	D	Normal.
Sibs.	x f	20	A MN 1	p	Imb.	I.Q. about 40.
Father.		57	OM	n	A	Normal: duodenal ulcer.
Mother		34 + 14	-	-	A	Normal: d. nephritis.
Sibs.	m) f)	0 + 28	-	-	-	Stillborn.
	f)	25	-	-	A	Normal.
	m)	$\frac{3}{12}$ + 25	-	-	-	Unknown: died fits.
	f	3 + 20	-	-	A	Normal: d. influenza.
	x f	18	OMN	p	Imb.	I.Q.20.
	m	17	OMN	-	A	Normal.
	m	15	OMN	-	A	Normal.
	-	- + 14	-	-	-	Miscarriage.
Father		39 + 1	-	-	D	Normal: d. alimentary cancer.
Mother.	≠	40	ON	n	A	Normal.
Sibs.	f.	18	ON	n	D	Normal.
	f.	15	ON	n	A	Normal.
	f.	13	ON	n	A	Normal.
	x m.	10	OMN	p	Idiot	I.Q.5.: epileptic.

Maternal half-sib of mother in family No. 16.

8.	Father.		82	ON	n	A	Normal.
	Mother.		67 + 11	-	-	D	Normal.
	Sibs.	m.	21 + ?	-	-	A	Normal: killed in war.
		f.	34 + ?	-	-	A	Normal: d. tetanus.
		m.	19 + ?	-	-	Idiot	Epileptic: probable phenylpetonuric.
		f.	2 + ?	-	-	-	Probably normal: d. bronchitis.
		m.	54	-	-	A	Normal (Unduly suspicious & antagonistic).
	x	m	52	A MN 1	p	Imb.	I.Q.36.
		f	51	A MN 1	p	Imb.	I.Q.43.: chronic gastritis
		f	49	-	-	A	Normal.
		f	47	BMN	n	A	Normal.
		m	43	A MN 1	p	Imb.	I.Q.40.
		m	37	A MN 1	n	S	Normal.
		m	35	BMN	n	D	Normal.
		f	32	BMN	n	A	Normal.
9.	Father.		36	OM	n	A	Normal.
	Mother.		38	A MN 1	n	A	Normal.
	Sibs.	m	15	A.M 1	p	Imb.	I.Q. about 20.
	x	f	11	A M 1	p	Imb.	I.Q.24: epileptic.
		f	7 + 1	-	p	Idiot	I.Q.4: epileptic.
		f	6	A M 1	n	A	Normal.
9.*	Father.		41	-	n	A	Normal.
	Mother.		37	ON	n	A	Normal.
	Sibs.	m	$\frac{2}{365}$ + 19	-	-	-	Unknown.
		m	18	-	-	A	Normal.
	x	m	15	OMN	p	Imb.	I.Q.30.
		m	13	ON	n	A	Normal.
		m	10	ON	n	A	Normal.

1.	Father.*	41	ON	n	A	Normal: Tb chest: duodenal ulcer.
	Mother.	36	BN	n	A	Normal.
	Sibs. f	18	-	-	A	Normal.
	f	$\frac{1}{12}$ + 15	-	-	-	Unknown: paralysed & deformed.
	m	14	-	-	A	Normal.
	m	13	BN	n	A	Normal: Tb chest.
	x m	11	BN	p	Imb.	I.Q.23
2.	Father.	41	OM	n	A	Psychopath.
	Mother.	36	ON	n	A	Normal.
	Sibs. m	$\frac{1}{12}$ + 11	-	-	-	Unknown: very weak and wasted.
	x m	10	OMN	p	Idiot	I.Q.4.: epileptic.
	m	2 + 7	-	-	A	Normal: d. pneumonia.
	m	6	OMN	n	A	Normal.
	m	4	OMN	p	Idiot	I.Q.12.
	f	2	OMN	n	A	Normal.
	f	1	OMN	n	A	Normal.
3.	Father.	44	OMN	n	A	Mild depression since 43.
	Mother.	36 + 1	-	-	A	Normal: d. nephritis.
	Sibs. x m	15	A MN 2	p	Imb.	I.Q.30.
	f	14	A MN 1	p	Imb.	
	m	0 + 4	-	-	-	Stillborn.
4.	Father.	64	BMN	n	A	Normal.
	Mother	60 + 10	-	-	A	Normal: d. hyperthyroidism.
	Sibs. x f	37	BN	p	Idiot	I.Q.2.
	-	- + ?	-	-	-	Miscarriage.

25					
Father.	43	-	-	-	Unknown.
Mother.	43	-	n	A	Normal.
Sibs. x m	21	OM	p	Idiot	I.Q.14.
26.					
Father.	75	ON	n	D	Normal (alcoholic).
Mother.	62 + 5	-	-	A	Normal: d. heart disease.
Sibs. m	0 + ?	-	-	-	Stillborn.
f	2 + ?	-	-	A	Normal: d. bronchitis.
m	43	-	-	A	Normal.
f	41	ON	p	Fm	I.Q.50.
f	39	ON	n	S	Normal.
f	37	-	n	A	Normal.
x m	35	ON	p	Fm	I.Q.50.
m	33	-	-	A	Normal.
f	31	ON	n	A	Normal.
m	26	ON	n	S	Normal.
f	23	-	-	A	Normal.
27.					
Father.	45	A MN 1	n	A	Normal.
Mother.	44	OMN	n	D	Normal.
Sibs. x f.	20	A MN 1	p	Idiot	I.Q.14.
m.	19	A M 1	n	A	Normal.
m.	- + 16	-	-	-	Miscarriage.
m.	- + 14	-	-	-	Miscarriage.
28					
Father.	34	ON	n	S	Frequent anxiety states: duodenal ulcer.
Mother.	32	A MN 1	n	S	Frequent anxiety states.
Sibs. x m.	8	A N 1	p	Idiot	I.Q.18.

9.	Father.	54	OMN	n	A	Normal.
	Mother	48	A M 2	n	A	Normal.
	Sibs. m	16	OM	n	S	Normal.
	x f	14	OMN	p	Idiot	I.Q.18.
10.	Father.	66	A M 1	n	D	Normal (Alcoholic).
	Mother.	59	A M 1	n	D	Normal.
	Sibs. m	37	A M 1	-	A	Normal. Hyperthyroidism.
	m	35	A M 1	n	Fm	I.Q. about 72.
	f	32	A M 1	-	A	Normal.
	x f	30	A M 1	p	Idiot	I.Q.14.
	m	28	A M 1	p	Idiot	I.Q.18.
	f	27	A M 1	n	D	Normal.
	f	23	-	n	A	Normal.
	f	22	A M 1	-	A	Normal.
	m	18 + 1	-	-	A	Normal.
	f	17	A M 1	n	A	Normal.
	f	15	A M 1	n	A	Normal.
	-	- + ?	-	-	-	Miscarriage.
11.	Father.	36	ON	-	A	Normal: Tb chest.
	Mother ≠.	36	A M 1	-	A	Normal.
	Sibs. x f	12	A MN 1	p	Idiot	I.Q.8.
	m	1 + 10.	-	-	-	Probably normal.
	f	8	OMN	-	A	Normal.
	f	6	OMN	-	A	Normal.
	m	$\frac{9}{12}$ + .2	-	-	-	Probably normal.

≠ Sib to mother in family No. 30.

Father.		55	ON	n	A	Normal: asthma, bronchitis.
Mother.		57	BN	n	A	Normal.
Sibs.	f.	27 + 4	-	-	Idiot	d. epileptic fits.) Probable
	f.	23 + 7	-	-	Idiot	d. bronchopneumonia.) Phenylketonuria.
	m.	26	BN	-	A	Normal.
	-	- + 24	-	-	-	Miscarriage.
	f.	1 + 22	-	-	A	Normal.
	x m	20	ON	p	Idiot	I.Q.16.
Father.		45	OMN	n	A	Normal.
Mother		48	OMN	n	A	Normal.
Sibs.	m	0 + 18	-	-	-	Stillborn.
	f	17	OM	p	Imb.	I.Q.30.
	x m	14	OMN	p	Idiot	I.Q.10.
	m	$\frac{2}{52}$ + 12	-	-	-	Unknown.
	m	9	ON	n	A	Normal.
Father.		45	OMN	n	A	Normal.
Mother.		42	A MN l	n	A	Normal.
Sibs	x m	16	OM	p	Idiot	I.Q.10: epileptic.
	m	12	A N l	p	Idiot	I.Q.8: epileptic.
	m	6	A MN l	-	A	Normal.
Father		65	OM	n	A	Normal: has cancer.
Mother		62	OM	n	A	Normal.
Sibs.	m	0 + ?	-	-	-	Stillborn.
	f	$\frac{2}{52}$ + ?	-	-	-	Unknown: three weeks' premature.
	m	31	OM	n	S	Normal.
	x f	27	OM	p	Idiot	I.Q.12.
	m	18	OM	p	Fm.	I.Q.64.

Father.		58	A MN 2	-	A	Normal: (Mild paranoid ideas.)
Mother.		59	A BM 1	-	A	Normal: gastric symptoms.
Sibs.	f	38	-	-	A	Normal.
	f	36	A BM 2	-	A	Normal.
	f	$\frac{10}{12}$ + 32	-	-	A	Normal: d. croup.
	f	30	A BMN 2	-	A	Normal.
	x m	28	A M 1	p	Idiot	I.Q.6.
	f	26	A M 1	-	A	Normal.
	f	24	A BMN 2	-	A	Normal.
	m	20	A BM 2	-	S	Normal.
	-	- + ?	-	-	-	Miscarriage.
	f	15	BM	p	Idiot	I.Q.10: epileptic.
Father.		45	ON	-	A	Normal.
Mother.		41	A MN 1	-	A	Normal.
Sibs.	-	- + 22	-	-	-	Miscarriage.
	m	19	OMN	p	Imb.	I.Q.25.
	x m	18	A MN 1	p	Idiot	I.Q.12: epileptic.
	m	$\frac{8}{12}$	ON	n	-	Appears normal.
Father.		33 + ?	-	-	A	Normal: died Tb.
Mother.		69 + 3	-	-	A	Normal: d. myocarditis.
Sibs.	x m	48	A M 1	p	Imb.	I.Q.35.

Father.		57 + 12	-	-	A	Normal: (alcoholic).
Mother.		59	ON	n	A	Normal.
Sibs.	f	$2\frac{6}{12}$ + ?	-	-	A	Probably normal.
	m	3 + ?	-	-	A	Probably normal.
	m	2 + ?	-	-	A	Probably normal.
	m	0 + ?	-	-	-	Stillborn.
	m	35	A MN 2	-	A	Normal.
	f	30 + 3	-	-	A	Normal.
	f	32	A MN 1	p	Imb.	Binet $6\frac{1}{2}$ years.
	m	30	A MN 2	n	A	Normal.
	f	28	A MN 2	-	A	Normal.
	f	24	A MN 2	n	A	Normal.
	m	21	A MN 2	n	A	Normal.
x	f	20	A MN 1	p	Idiot	I.Q.20.
	m	18	A MN 1	p	Imb.	I.Q.40.
Father.		51 + 2	-	-	A	Normal: chronic gastric symptoms.
Mother.		43 + 7	-	-	A	Normal: d. Tb.
Sibs.	f	25	BM	-	A	Normal.
x	f	24	A M 1	p	Idiot	I.Q.18: epileptic.
	f	21	BM	-	A	Normal.
	f	1 + 19	-	-	-	Mentally defective: probable phenylketonuric.
	f	16	BM	-	A	Normal.
	f	13	BM	-	A	Normal.
	f	8	A M 1	p	Idiot	I.Q.16.

1.	Father.		56	OMN	-	A	Normal.
	Mother.		55	A N 1	-	A	Normal.
	Sibs.	f	5 + 27	-	-	Idiot	Epileptic: probable phenylketonuric.
		f	11 + ?	-	-	Idiot	Probable phenylketonuric.
		m	30	-	-	A	Normal.
		f	28	OMN	n	S	Normal
		x f	25	OMN	p	Idiot	I.Q.6.
		m	19	A MN 1	n	A	Normal.
		m)	15	ON	n	A	Normal.
		f)	1 + 14	-	-	A	Normal.
2.	Father.		41	OMN	-	A	Psychopath.
	Mother.		36 + 11	-	-	A	Normal.
	Sibs.	f	18	BMN	-	A	Normal.
		x m)	16	BN	p	Idiot	I.Q.10) probably
		m)	16	BN	p	Idiot	I.Q.10) monovular.
3.	Father.		59 + 7	-	-	A	Chronic alcoholic: paranoid ideas after 50: d. cancer.
	Mother.		64	A M 2	-	A	Normal (unduly suspicious).
	Sibs.	f	8/12 + 41	-	-	A	Unknown.
		f	41	OMN	-	S	Thyroid removed at 35 for exophthalmic goitre.
		x f	38	OMN	p	Imb.	I.Q.21.
		m	37	OMN	-	A	Normal: gastric ulcer.
		m	33	OMN	p	Imb.	I.Q.40.
		f	30	A MN 2	-	A	Normal.
		m	28	-	-	A	Normal.
		m	26	-	-	A	Normal.
		f	24	A MN 2	p	Imb.	I.Q.43.
		m	22	-	-	A	Normal.
		f	19	A MN 2	-	A	Normal.

Father.		38 + 22	-	-	A	Normal: killed in war.
Mother.		60	BMN	-	A	Normal.
Sibs.	f	$1\frac{6}{12}$ + 39	-	-	-	Normal: d. bronchopneumonia.
	f	39	A MN 1	-	A	Normal.
	m	$\frac{2}{52}$ + 36	-	-	-	Unknown.
	m	$\frac{2}{52}$ + 34	-	-	-	Unknown: premature.
	x m	28	A BN 1	p	Imb.	I.Q.25.
	f	3 + 22	-	-	Idiot	Probable phenylketonuric: d. pneumonia.
Parents.		-	-	-	-	Unknown.
Sibs.	m)	31	ON	n	A	Normal.
	x f)		ON	p	Fm	I.Q.61
Father.		51	A MN 1	n	A	Normal.
Mother.		52	BMN	n	A	Normal.
Sibs.	f	0 + 23	-	-	-	Stillborn.
	m	21	A MN 1	p	Imb.	I.Q.34.
	f	19	BMN	n	A	Normal.
	f	$\frac{1}{12}$ + 16	-	-	-	Unknown.
	f	13	BM	p	Fm	I.Q.70.
	f	12	BMN	n	A	Normal.
	m	10	OMN	p	Fm	I.Q. about 50.
	x f	8	BM	p	Idiot	I.Q.10: epileptic.

Appendix II.

Clinical Notes

on the Phenylketonuric Patients and on their abnormal relatives.

y 1. A family from rural Suffolk. Parents live in timbered cottage in tiny village; father a coachman.

Propositus 1. Male, born 19.9.15. History. Full time normal birth, gross defect soon noticed, never walked or talked; teeth appeared early but soon decayed; one epileptic fit at age 14. Examination in R.E.C.I. at 24. Behaviour, gross idiot, cannot stand, no speech, can do nothing for himself, shows some appreciation on being fed, incontinent, no smell noticed. Physical: Head 142: 175: 0.81. short but broad, broad chest with extreme lumbar kyphosis, moderate fair hair, irides brown, widely spaced incisor teeth, three small raised grey nodules in skin of back, pigmented skin patch on forehead, nodules visible and palpable on great auricular nerves, microphthalmos with old iritis, bilateral cataract, now blind, slight corneal opacities, lies in universal flexion, limbs wasted, slight contractures but legs can be extended, slight spasticity in legs, knee and ankle jerks exaggerated, plantars flexor, forearms wasted, wrist donus. Genitals small, testes undescended. Urine positive.

Sib. Male born 3.7.29. History. Full time normal birth, very weak infant, many fits since infancy, often several a day, twitching and slight loss of consciousness, usually very constipated. Examination in R.E.C.I. at 9 yrs. 5 mons. A very small, emaciated weak idiot, habits defective, has to be fed, unable to speak or walk, pays little attention, resents interference. Physical: Head 142: 165: 0.86. Fair hair, pale blue eyes, widely spaced incisor teeth, cranial nerves normal, retinae healthy, all tendon reflexes exaggerated, plantars flexor, no spasticity, legs held in talipes position. Genitals very small, undescended testes. Typical smell noticed. Urine positive. Died at 9 yrs. 7 mons. of bronchopneumonia. Multiple small neurofibromata on all nerves; signs of chronic slight cerebral oedema with dying nerve cells. Thyroid small and fibrous. Case notes and Postmortem report published by Penrose.

Father. 66. Examined. Paranoid delusions since late fifties. Coachman out of work; thinks men in village point at him and hint he is lazy; reserved and unsociable, sometimes very sad for days thinking his wife is poisoning him.

Father's father. For many years before death at 83 he had delusions that people were attempting to poison him.

ly 2. A large family from rural Essex, containing two cousin marriages with affected offspring.
Propositus 2. Female born 23.5.94. History. Normal pregnancy and birth; defect noticed at about 18 months; fairly easily managed at home; at school for a short time but learnt nothing; no fits, walked at 2, talked at 5, always easily excited. Examination in R.E.C.I. at 44 . Behaviour. Imbecile, Binet 4 years, clean in habits, can knit, talkative, but uses words in wrong senses, always hungry. Physical. Head 140: 177: 0.79. Well developed, pleasant facies (see photograph), many wrinkles, fair hair, blue eyes, many small moles and several small wart-like papillomata on skin of trunk, neck, face. Broad chest with slight kyphosis. Menses normal. Tendon reflexes exaggerated, no spasticity, plantars flexor. No nodules felt on nerves. Urine positive.

Sib. Female, born 28.6.00, Admitted R.E.C.I. at age 10 and died at age 15: an idiot, spoke only few words, could not use a spoon, had muscular weakness in legs. Probable phenylketonuria

Father. died 70. A farm labourer. From age 44 slowly became more reserved, inactive, gloomy, sad and did no work. Symptoms varied, slowly increased. He felt "fed up with himself" and feared to be alone. Nephritis appeared and he died of cerebral haemorrhage.

Father's Mother died 77, Mild psychosis from age 75. Became afraid to let strangers see her, kept to her house, "talked funny", and often went to bed.

Mother's Father. Farm labourer; admitted to Mental Hospital aged 50 in deep depression; died in hospital aged 83.

Maternal uncle. Unknown psychosis, onset at 51 with depression, hallucinations and attempt at suicide; some improvement after 4 years, then deteriorated and had epileptiform seizures before death at 58.

ly 2 a. Part of Family 2; see chart in Appendix IV.

Propositus 2 a. Female, died 4 years; idiot, never sat up, had to be fed, probable phenylketonuric.

Sib. Female died 4 years; idiot, similar, probably phenylketonuric.

Sib. Female, examined in Suffolk Mental Hospital at age 59. Personality. Average intelligence. Rather shy and quiet, less robust and less hearty than her sibs, a regular and devout church-goer, very conscientious, a capable wife and housekeeper, hard working and very affectionate to her relatives, Never very cheerful and easily depressed by bad weather or small domestic worries. Psychosis. She was well until age 48 when she was quite overwhelmed by the sudden death of her husband. Within two weeks of his death she was admitted to the mental hospital, agitated, restless, depressed, apprehensive, shouting "the end of the world has come, I shall never wake up again; oh, what shall I do, everything is racing on - oh - and the black past". She had threatened suicide. On admission there was some gastro-intestinal disturbance. She had a furred tongue, marked constipation, abdominal pain and pyrexia of 100. She tended to retain her urine. Symptoms of confusion and disorientation became prominent. For two weeks she was in a drowsy semi-stupor. Her bodily health and her confusion then improved, but within a month she had suffered attacks of cystitis and paratyphoid fever. Her depression continued; "she might as well die". After recovery from her fever she became increasingly resistive to nursing attention, lying flexed beneath the bed-clothes, with eyes shut, and shouting foul curses at anyone who roused her. Her habits were defective. She had to be fed. In the ten years since her admission these resistive symptoms have been prominent, and have masked her depression. At age 59 she lies motionless and silent in bed, doing nothing for herself. On being spoken to or touched she offers resistance, some active negativism, and indulges in much swearing of an anal-erotic trend; "ass-holes to you, bugger you, go to the devil". She insists that she is dead. Tears or laughter never occur. She will not cooperate in the examination of her sensorium. She is quite observant of ward routine, recognises doctors and nurses as such, and there is probably no gross disorder of her memory. She is thin and has developed contractures of the hamstrings and forearm flexors. She has a marked permanent malar flush, a moderate growth of hair on the chin and upper lip, and there are two small yellowish raised wart-like structures in the skin on the forehead. There are no neurological abnormalities. The heart and lungs are healthy. The right pleura is thickened from an old pleurisy. There is no radial arteriosclerosis.

The urine is of average specific gravity and does not contain albumen, sugar or acetone or phenylpyruvic acid. Died 61, chronic subacute septicaemia, bed sores and terminal bronchopneumonia.

Sib. Female , died 54. Depressive psychosis. She was a hard working generous girl, could read and write but was "not clever" and so stayed at home to look after her parents. She appeared contented until they died, when she became distressed, tearful and talked of going into the pond. She married at 50, having known her husband 5 years. After marriage she became worse, "very strange and difficult for a while". She said her husband was no good, never pleased her; she tired easily, did little work, complained of strength going out of her legs. Later she and her husband went to live in the house of her brother-in-law of whom she became unduly jealous, opening and returning letters and parcels sent to him. She did no work, would often shut herself in her room for a whole day; she wept much but expressed no delusions. She was agitated. She attempted suicide several times, and when her brother-in-law married again she committed suicide at 54.
An account of this family has been published by Penrose.

y 3. A family from an Essex village, happy home atmosphere.

Propositus 3. Male born 12.5.23. History. Normal pregnancy and birth, healthy infant but did not walk until 5. Infrequent major epileptic fits began at 5, never at school. Examination in R.E.C.I at 16. Behaviour. Low grade idiot, pays little attention, incontinent, no speech, cannot feed himself, no smell noticed. Physical. Head 140: 189: 0.74; short broad stocky build, slight kyphosis, light brown hair, brown eyes, large area of dark brown pigmentation over right scapula, a few raised whitish skin spots, all tendon reflexes exaggerated, no spasticity, plantars flexor, thyroid and genitals normal, the left median, ulnar radial and musculo-cutanious nerves were surgically exposed above the elbow and found to be free of nodules. Urine positive.

Sib. Male born 1916. History always backward, but less so than propositus. Examination at home at 23. Behaviour. Imbecile M.A. 5 - 6 years, placid, content, amenable, can wash and dress himself and do simple house jobs. Roams the village alone, never in trouble. No fits. Formerly easily excited and made talkative. Physical. Height 5 ft. 7½ in. Head 149: 200: 0.75; well developed, muscular, pleasant facies, medium fair hair, pale brown eyes, no abnormal spots, no nodules felt on nerves, tendon reflexes all exaggerated, plantars flexor, no spasticity, characteristic smell noticed. Urine positive.

Sib. Female born 22.8.19. History Very backward, walked at 3, never talked, no fits. Examination in R.E.C.I. at 20. Behaviour Idiot, no speech, hums vague tunes and sits rocking to and fro, can run unsteadily, habits defective, can feed herself, no smell noticed. Physical. short broad habitus, weight 100 lbs: moderate fair hair, pale brown irides with reddish spots, thyroid and genitals normal, all tendon reflexes exaggerated, legs slightly spastic, plantars flexor, widely spaced teeth. Urine positive.

Sib. Female born 12.24. Examination at home at 15. Dull intellect but not defective. Urine negative. Marked general underdevelopment, small hands and feet, all in proportion. Jan: 1930 weight 34 lbs: Height 3 ft. 2 in. May 1935 weight 49 lbs: height 4 ft. July 1939 height 4 ft.7 ins. No evidence of diabetes insipidus.

ly 4. A Cornish family. Parents in London suburb.

Propositus 4. Male born 12.6.06. History Severe vomiting during 3rd and 4th months of pregnancy, defect noticed at birth; a gross idiot, quite helpless, walked late, never talked, incontinent, objectionable smell, two convulsions while teething. Examination in Leavesdon Mental Hospital at 33. Low grade idiot, dribbles saliva, incontinent, no speech, can feed with his fingers, can walk, pays little attention. Physical. Head 135: 185: 0.73. Underdeveloped, coarse features, moderate fair hair, blue eyes, many small brown spots up to 2 mm diameter particularly on trunk and thighs, two larger and slightly raised. Thyroid normal size. Genitals and testes small. Hands and feet always blue and cold. Tendon reflexes of arms and legs are exaggerated, plantars flexor. Right great auricular nerve is palpable but not visible, as a slightly nodulated cord. Urine positive.

Sib. Female born 1910. History quite similar to that of propositus 4 including a few teething convulsions. Examination in Cornwall Mental Hospital at 29. Behaviour. Irritable, easily angered, low grade idiot, resents examination, screams, incontinent, no speech, can use a spoon, inactive, sits about. Physical. Height 57 ins. Head 139: 185: 0.75. Broad and short, clumsy gait with stoop, typical smell, coarse facies, fair golden hair, hazel eyes, many freckles on face forearms hands neck and thorax. Eight pigmented nodules on face, multiple warts on left hand, raised dark brown 5 mm papilloma on left forearm, much brown pigmentation on trunk, no thyroid disturbance, menstruation regular, tendon reflexes exaggerated especially in left leg, left ankle clonus, left plantar extensor, right flexor. Urine positive.

Father. died 48. Psychopath. A clever and eccentric schoolmaster, "lacked balance and common sense", secretive and irresponsible with money; became much more eccentric in forties, told absurd tales of his wealth, left his work, lived in squalor and died of "syphilitic gumma of brain".

Father's father died 59. Unknown psychosis: "lost his memory and had senile decay".

Mother's mother 72 Examined at home. Hypomania for at least 4 years: elated, overtalkative, unduly friendly and irritable, maintains she is exceptionally gifted.

ly 5. A scattered family of French Huguenot descent.

Propositus 5. Female born 18?0. History Few facts known, little schooling, never able to work, cared for at home until death of mother, clean in habits, amused herself but had violent tempers. Examined in Leavesdon Mental Hospital at age 65 by L.S.Penrose. Idiot grade, Height 4 ft 10½ ins. Head 135: 184: 0.73. Dorsal kyphosis, hyperthyroidism, tendon reflexes rather brisk, several pigmented spots on trunk, small skin tumour on back of thigh. Urine positive. Died at 67. Postmortem by Dr R.M.Stewart. Cachexia carcinoma of thyroid with mediastinal metastases: cerebral oedema

Sib. Female died 64 Mild depression from age 50; remained unduly sad and inactive but was able to look after her house, no history of delusions.

Sib. Male died 48. Unknown psychosis, onset in forties with severe alcoholism, became miserable and took his life.

Sib. Male died 64. Intermittent psychosis from 28. Unstable, unreliable, worked only when he liked. Said that gangs of men followed him in streets. Sometimes he was excessively devout, religious, temperate; at other times alcoholic. In later years he said many people were after him, became sad and took his life.

Sib. Female died 50. Depression at 45; lost confidence, felt she did not do her best in the home, felt "everything going wrong with her". Improved much; acute relapse at 47 with tearful agitation, restless activity, hopelessness, suicide in front of train.

y 6. A family scattered in London suburbs.

Propositus 6. Female born 19.6.88. History largely unknown; used to have major epileptic fits about once a week. Examination in Leavesden Mental Hospital at 51. Behaviour: idiot, no speech, defective habits. Physical: Head 134: 178: 0.75. Thin, coarse featured, slight kyphosis, narrow chest, thyroid normal, menses ceased at 46, no fits in hospital, wasting and weakness of quadriceps and to slight extent of hamstrings, especially on left, no spasticity, unable to walk without slight support, slight wasting of left upper arm. Tendon reflexes exaggerated. Left plantar extensor, right flexor. Feet blue and cold. A few small brown spots on trunk, one raised, wart-like. Marked coarse tremor of whole body, including head. No nodules felt on nerves. Urine positive.

Sib. Female 45 examined. Acute depression at 33 for one year: felt very sad, wept, fit for nothing, life not worth living, at end of everything, could not do housework, afraid of everything, of Asylum, of going insane. Recovered well and at 45 had mild recurrence for 2 months. No manic periods.

ly 7. Parents unknown, probably Cornish.

Propositus 7. Female born 8.12.03. History. Facts unknown. Examination in Leavesden Mental Hospital at 41. Behaviour. Imbecile grade, clean and tidy, fair speech, washes and dresses herself, can sew a little. Complaint of pain in head. Fainted once for no obvious reason. No fits. Physical: Head 132: 179: 0.74. Fair hair, no spots, some kyphosis with broad chest, menses normal, thyroid very small, tendon reflexes exaggerated, plantars flexor.

Sib. Female 36 examined. Certified feeble minded, I.Q. 70. Boarded out as domestic, happy, contented, short, underdeveloped, not phenylketonuric

y 8. A scattered family, some in London.

Propositus 8. Female born 3.9.03. History: Facts unknown. Examination in Leavesden Mental Hospital at 36. Idiot, has a few words, can feed herself. No fits. Head 139: 181: 0.77. Well developed, moderate fair hair, a few small brown skin spots, thyroid and menses normal, all tendon reflexes exaggerated, plantars flexor.

Maternal uncle; psychopath; pathological liar, rover, drunkard, cadger, in a reformatory at one time.

y 9. An Aberdeenshire family; parents hard working labouring folk.

Propositus 9. Female born 17.1.30. History. Mother had severe vomiting and anaemia during pregnancy; full time birth, was a strong infant though had measles very severely, never talked, walked unsteadily at 4, always very constipated, from age 3 months had occasional "turns" in which she would stare at the roof for a few seconds, never any twitching. Examination in R.S.N.I. at 8 yrs. 10 mons. Low grade idiot, scarcely recognises nurses, has to be fed, no speech, incontinence of bladder and bowel, no abnormal smell noticed, much variation in mood, happy, contented, then crying and screaming attacks. Physical: Height 44 ins. weight 50 lbs. Head 132: 173: 0.76. Quite well developed, moderate fair hair, deep brown irides, numerous pale yellow freckles below eyes and 19 spots on limbs, oval, dark brown, slightly raised, with no hair growth, largest about 3 by 2 mm. Incisor teeth widely spaced with deficient enamel, thyroid and genitals normal, all tendon reflexes exaggerated, persistent ankle clonus and double extensor responses. No spasticity. Can walk. No nodules felt on nerves. Urine positive.

y 10. A family from East Sutherlandshire.

Propositus 10. Female born 12.6.07. History. Pregnancy and birth normal, walked at one year, never talked, few major fits in infancy. Examination in R.S.N.I. at 30. Behaviour: Obvious idiot, no cooperation, no speech, cannot dress herself, habits clean and can feed with a spoon, understands a few simple commands such as "go to bed", likes radio, hums tunes and appears to know them, usually placid and distinctly happy, she has outbursts of screaming temper. No fits in hospital. Menses regular, 2 to 3 days duration, faeces noticeably pale, no smell noticed. Physical: Height 58¼ ins. weight 97½ lbs: Head 138: 182: 0.76. Broad stocky build, dark brown hair, blue green eyes, upper incisors wide spaced, one small wrinkled papilloma on skin of back, thyroid normal, breasts and pudenda well developed, tendon reflexes brisk in arms, increased in legs with knee and ankle clonus, plantars flexor. No nodules felt on nerves. Urine positive.

Sib. Female born 9.2.03, died in R.S.N.I. aged 15 of pneumonia. A helpless idiot, probable phenylketonuria

ly 11. A large family in industrial Stirlingshire with relatives in North Ireland.

Propositus 11. Female born 22.8.23. History. An idiot from birth, occasional major fits from infancy. Examination in R.S.N.I. at 15 yrs. 1 mon. Behaviour: Low grade idiot, pays almost no attention, does not follow light with eyes, has to be fed, washed and dressed, no speech, defective habits, rare major epileptic fits, restless, often screams at meals, does not recognise nurses, no smell noticed. Physical: Height 58 ins. weight 90 lbs: Head 144: 185: 0.72. Well developed, fair hair, green-blue eyes, no spots, upper incisor teeth separated, hands unduly large and feet unduly small, tuberculous glands in neck, genitals well developed but menses not begun, tendon reflexes unduly brisk with some left ankle clonus, legs slightly spastic, plantars flexor. No nodules felt on nerves. Urine positive.

Sib. Male died 4, mental defective, very little speech, played little, good bodily development, very fair hair, tuberculous foot, died ? Tb meningitis. Probable phenylketonuric

Sib. Male died 10. Examined at home at 9 yrs. 7 mons. Normal intelligence, tiny boy, well proportioned, height 41 ins. weight 39 lbs: Head 135: 169: 0.80, always unduly thirsty and passes large quantities of pale urine, specific gravity 1007, no abnormal constituents. Admitted for investigation to Royal Infirmary of Edinburgh, but died of appendicular abcess. Average fluid intake 1800 c c, urinary output 1900 c c. Query diabetes insipidus.

Father 58, examined. Chronic anxiety state. Always a worrier, worse in recent years, greatly upset by daughter having illegitimate child, thought he was dying, improved quickly.

Father's mother. Anxiety state. Always unduly anxious and frightened.

Paternal uncle. 54. Mild depression since 50. Has not worked since. Always agitated and worried about himself and future, sleepless. Symptoms wax and wane. At one time he thought he was dying, had great fear, and gastric symptoms. Doctor says he has no hyperthyroidism

Paternal aunt died 1932 age 46. Gradual onset of psychosis at 40, sleepless, lost weight, could not manage work, sad, cried much. Admitted at 45 to Stirling District Mental Hospital, confused, incoherent, resistive, thin, anaemic. Some months later she had tremors of hands, face and tongue, difficulty in swallowing, gastritis and diarrhoea. Confusion increased to death. Diagnosis: Toxic-confusion, possible hyperthyroidism. This woman married her first cousin and had a son, aged 18, whom I saw but could not examine; short, underdeveloped, feeble minded, did poorly at school, done no work since, slight stammer. Good bodily health. Urine not obtainable.

Paternal uncle 49, examined. Hyperthyroidism for some years. Marked exophthalmos, sweating, fine tremor, brisk tendon reflexes, enlarged thyroid, loss of weight. Complains that "noises make him jump" and he is "all of a tremble" if excited.

Paternal aunt died 46 of exophthalmic goitre with heart affection, 4 years duration.

Paternal aunt died 28 after operation for exophthalmic goitre.

Paternal uncle 35 examined. Anxious hypochondriac, always going to his doctor with vague aches and pains, excessive worry. At times well composed. No sign of hyperthyroidism.

ly 12. A family from Shetland Isles.

Propositus 12. Female born 11.3.22. History. Normal pregnancy and birth, did not thrive, slight convulsive seizures began about 12 mons. continued for a few years; walked at 2, spoke a few single words at 10 always very constipated, no smell noticed. Examination in R.S.N.I. at 16. Behaviour: Idiot grade, no speech, hums and recognises tunes, very restless, active, impulsive, destructive, wild screaming if annoyed, can use a spoon and fork, clean habits without prompting. Menses regular and normal, began at 13yrs. 3 mons., frequent masturbation. Physical: Height 62¼ ins. Weight 106 lbs. Head 144: 181: 0.80. Well developed good looking girl, rosy cheeks, moderate fair h hair, blue-green eyes wide spaced, lower incisors wide spaced, broad chest with kyphosis on walking, genitals normal, overdeveloped breasts, thyroid normal, one small raised spot below right eye and one on chest, tendon reflexes exaggerated, plantars flexor, no nodules felt on nerves, urine positive

ly 13. A large family of Devon rural folk.

Propositus 13. Female born 25.9.27. History. Normal pregnancy and birth, a miserable weakly infant, no fits, walked at 2½, a few words at 6. Examination in R.W.C.I. at 10 yrs. 7 mons. Behaviour: Imbecile, Binet- Simon age about 3. Little speech, but obeys simple commands, can dress and undress, use spoon and cup, imitates the fits of epileptics and teaches idiots to walk, restless, easily frightened, violent temper, left handed "mirror" writing from right to left, cannot write letters or read, clean habits. Physical: Height 5 ft. 6 ins. Weight 62¾ lbs. Head 14: 175: 0.80. Well developed, comely, fair hair, light brown eyes, marked variable squint, widely spaced incisor teeth, hands unduly small with tapering fingers, a few freckles, no spots, very offensive stool, tendon reflexes normal.

Mother, 32, examined at home. Chronic anxiety state since 21, increased by husband's infidelity. Always worried, wants to cry, miserable if alone, never deep sadness, easily excited, complains of heart fluttering, stinging on top of head coming up from back of neck, "rheumatism" in shoulders, colitis. No sign of hyperthyroidism.

Mother's mother. Hypochondriacal invalid who likes to stay in bed; vague pains.

Maternal uncle, 33, examined. Anxiety state with possible hyperthyroidism. Intelligent active man. Press of activity, must always be doing something, tires himself in garden after work. Unreasonably worried about security of job; becomes "all tense and shaking", sleepless, tense feeling in head and pain over heart. Feels warm, even on cold days. No tremors, no exophthalmos, pulse 92, thyroid slightly enlarged.

Maternal uncle, 23, Many neurotic symptoms since teens; vague pains and a soft place on top of head that burns and stings. Deserter from Army and often in police hands.

Paternal great-uncle. Imbecile, type undetermined, not phenylketonuric.

Paternal great-uncle, 44, examined in Plymouth Mental Hospital, Devon. Psychosis began at 32 with emotional turmoil and excitement. At times he attempted suicide, at times he was grandiose, had associated with royalty, was the son of God, made sign of cross with his own blood, saw visions and heard voices of kings and queens. He became increasingly preoccupied and unemployable. At 44 the acute symptoms have regressed. He has settled down well to hospital life and farm work. His intellect and memory show little impairment; he is in good touch with his situation and answers briskly and to the point. There is little emotional response,- a shallow apathetic acceptance of everything. He denies his former delusions, and now only occasionally hears voices,- his wife telling him to "get well and come out". Classed as Schizophrenic psychosis.

14. A large family of Devon labourers.

Propositus 14. Male born 20.3.25. History. Mother very nervous during pregnancy, some uterine haemorrhage before his birth at full time; very large and fat infant, severe indigestion with vomiting for years, no fits, walked at 18 months, never talked. Examination in Church Home, Exeter at 11. Behaviour: Idiot, walks very unsteadily, cannot speak or dress himself, incontinence of bladder and bowel, eats with fingers, happy. Physical: Height 4 ft 6½ ins. Weight 63 lbs. broad round head, fair hair, light brown eyes, widely spaced teeth, broad chest, about 120 small moles on body, thyroid and genitals normal, tendon reflexes normal, stools always loose, pale, with very offensive smell. Urine positive.

Sib. Male born 6.33. History. Normal pregnancy and birth, walked at 3, scarcely talked, good digestion, no fits. Examination at home at 5 yrs. Behaviour: imbecile, I.Q. about 40, restless, active, much curiosity, usually happy, wild screaming if annoyed, destructive, runs easily, clumsy movements, no constructive play, says a few words only. Physical: Head 128: 170: 0.75. Well developed, pretty, very fair hair, brown eyes, five moles on body, nervous system, thyroid and genitals normal. No smell noticed. Urine positive.

Mother 39, examined. Anxiety state from 35 for 3 years. Had very marked anxious forebodings for no external reason; would worry and wonder what would become of her children if she died or if husband lost work; was sleepless, "all tense", and wept much. No sign of hyperthyroidism at 39.

Paternal uncle, 43, Anxiety state. Gastric symptoms for years, severe cardio spasm at 39 for some months, was much alarmed about himself. Always timid and solitary, he now worries much, especially at night.

y 15. Propositus illegitimate: mother's ancestors are Devon rural workers.

Propositus 15. Female born 22.12.28. History. Normal pregnancy and birth, dull placid infant, walked at 3½, talked very late, much vomiting in infancy, no fits. Examination in Church Home, Exeter at 20. Behaviour: High grade imbecile, Binet I.Q. about 40, unduly quick in her emotions, wild, excitable, easily upset, understands simple commands well, speech slurred. Physical: Height 62 ins. Weight 100 lbs. Head 140: 185: 0.76. Well developed, tall and slim, fair hair, ten warts on hands and feet, one pedunculated skin lobule on neck, definite uniform enlargement of thyroid, no signs of hyperthyroidism, tendon reflexes slightly exaggerated, menses normal, no smell noticed, urine positive.

Maternal aunt, 40, examined at home. Anxiety neurosis. Always high strung, anxious type. At 36 spent 18 months at home, often in bed, with "heart and nerves", great weakness and palpitation. Medical opinion was neurosis. Improved recently but often easily worried; attacks of palpitation at night with fear that she is dying. No sign of hyperthyroidism.

Maternal uncle, 35, examined in P.A.I. Exeter. Feeble minded epileptic, not phenylketonuric. Underdeveloped man, fits since boyhood, did badly at school, labouring jobs. Now a deteriorated epileptic with series of fits every 3 or 4 weeks, mostly at night.

Maternal great uncle, imbecile, "born real silly, never worked".

ly 16. A large family of Devon rural labourers.

Propositus 16. Female born 18.1.20. History. Normal pregnancy and birth, never talked, walked at 3, occasional slight muscular twitchings in infancy and a few major epileptic fits later. Examination in Church Home, Exeter at 18. Behaviour: low grade imbecile, Binet I.Q. 20, uses a spoon, cannot dress, habits clean with attention, understands a little, placid. Physical: Height 57½ ins. Weight 98 lbs. Head 151: 173: 0.87. Broad and fat, broad chest, moderate fair hair, blue eyes, a few freckles, tendon reflexes exaggerated, plantars flexor, menses normal, no smell noticed, urine positive.

Mother's father died in mental hospital, unknown psychosis.

Maternal first cousin, female age 17, examined in R.W.C.I.. Feeble minded, Binet 8 years, fat lethargic, slow, not phenylketonuric

ly 17. Related to family 16.

Propositus 17. Male born 1.7.28. History. Normal pregnancy and birth, infantile jaundice, never walked or talked, frequent myoclonus began at 12 months and major epileptic fits at 3 years. Examination in Church Home, Exeter at 10 years. Low grade idiot, helpless, cannot stand or sit, recognises nothing, not even food, which however is swallowed when put in mouth, throws himself about, incontinent, major epileptic fits about 4 each day, by day and night, infrequent petit mal, also sudden harsh transient screams. Physical: Head 135: 171: 0.79. Quite well developed, but legs and feet are small, very fair hair, eyes wide apart, teeth widely spaced, 31 small brown spots on body, numerous freckles, thyroid and genitals normal, tendon reflexes

normal, plantars flexor, objectionable smell, particularly faeces, urine positive.

Mother's father, Unknown psychosis, died aged 37 in mental hospital.

Maternal great-aunt, 49, examined in Devon Mental Hospital. Undiagnosed psychosis, query organic. At 43, soon after birth of last child, she became sad and inactive, neglected her house and sat brooding. She believed she had a growth in her throat, complained of headaches. Admitted to hospital excited and violent, thought herself wealthy, and had devised a cure for unemployment. Slowly quietened, but had frequent attacks of rage and violence. From age 43 she had infrequent attacks simulating petit mal. At 49 she is deteriorated, incooperative, unemployable, inattentive, has vague persecutory delusions and some intellectual deterioration.

y 18. A large family in rural Somerset.

Propositus 18. Male born 25.12.86. History. Few facts known; was at school for a few years, but learnt nothing, no fits. Examination in P.A.I. Somerset at 52. Behaviour: quiet placid imbecile, Binet I.Q. 36, capable only of floor polishing, dresses and washes himself and is clean, unable to read or write any letters, or tell the time. Physical: Height 66 ins. Head 144: 186: 0.77. Well developed, asthenic habitus, looks older than his years, walks with slight kyphosis, very fair hair, blue eyes, much psoriasis, one small skin nodule on left elbow, arteries thickened, pulse slow, tongue tremulous, some finger tremor, optic fundi normal, extensors and calf muscles of left leg wasted, left knee and ankle jerks exaggerated and plantar extensor, tendon reflexes in right leg and arms brisk, right plantar flexor. No nodules felt on nerves. Urine positive.

Sib. Male died 19. Mother had poor health during pregnancy; a helpless idiot, occasional major epileptic fits, legs and arms were stiff and contracted so he could not walk or feed himself.

Sib. Female 51. History. Contented, placid, inactive imbecile, kept at home, can wash dishes and make beds, occasional attacks of dyspepsia with vomiting, ill for several months in one attack, no fits. Examination at home at 51. Imbecile, Binet I.Q. 43; Burt's Reading Test 6.2 years, poor vocabulary. Physical: thin small short, fair hair going white, one hairy pigmented mole on chin, one skin lobule on upper eyelid. No abnormality in nervous system. Menses ceased, were regular. Urine positive.

Sib. Male 43. History. Few facts known, no fits, a placid imbecile kept at home, goes alone to work in friend's bakery, where he stokes furnace and cleans tins under supervision. Examination at home at 43. Imbecile, Binet I.Q.40, understands simple commands well, has simple speech, cannot read or write. Physical: Height 61½ ins. Head 136: 181: 0.75. Short but muscular man, broad chest, ungainly gait with slight kyphosis, fine tremor of hands and tongue but no sign of hyperthyroidism, much chronic psoriasis, fair hair, three raised yellow spots on right arm, some spasticity of legs with exaggerated knee and ankle jerks and double extensor responses. No smell noticed. Urine positive.

19. An extensive family of farm labourers in the Cotswold country.

Propositus 19. Female born 1927. History. Normal pregnancy and full time birth, walked at 4, no attempts to speak, infrequent major and minor epileptic fits from age 3. Examination in Oxford Mental Hospital at 11. Behaviour: Imbecile, Binet I.Q. about 24, no speech, hums and recognises tunes, obeys simple commands, usually cheerful, often overactive and irritable, feeds herself, habits often defective. Physical: Head 146: 191: 0.76. Stocky build, comely rosy cheeks, well nourished, very broad chest, broad face, eyes set far apart, very fair hair, bright blue eyes with grey white anterior pigments, teeth good, upper incisors separated, thyroid and genitals normal, no nodules felt on nerves, runs unsteadily, left hand and foot smaller than right, tendon reflexes normal, left plantar extensor, right is flexor. No smell noticed. Urine positive.

Sib. Male born 20.9.23. History. Normal pregnancy and full time birth, walked at 14 months, a few words at 2, habits defective until 7, never at school, no fits. Examination at home at 15. Behaviour: Placid, happy, contented inactive imbecile, I.Q. 20, saws wood and carries coal. Physical: Height 64 ins. Head 150: 194: 0.77. Tall muscular good looking healthy boy, very fair hair and blue eyes, markedly broad chest with slight kyphosis, no abnormality in nervous system, thyroid and genitals normal, no smell noted, no nodules felt on nerves. Urine positive.

Sib. Female died 7 on 11.5.37. History. Normal pregnancy and full time birth. Mother noticed defect at 6 months; child never showed any interest, never walked or talked, infrequent major epileptic fits from age 4. Examination in Oxford Mental Hospital at 6 yrs. 10 mons. Head 130: 171: 0.76. A small underdeveloped idiot, can sit up, cannot stand, pays little attention, does not follow light, expresses pleasure at food, incontinent, severe wasting and spasticity of lower limbs with flexor contractures, exaggerated tendon reflexes and extensor plantar responses. No smell noticed, urine positive. Three moles on trunk. Died of bronchopneumonia. Postmortem showed some chronic internal hydrocephalus with hyperaemia of cerebral cortex. Nerves not examined.

Maternal aunt, 48, examined. Encephalitis lethargica at 36, now marked striatal rigidity with slight mental enfeeblement.

Maternal great-aunt. Senile psychosis, onset 86, feeble health, arteriosclerosis, confused, restless, wanders, mutters querulously, deficient comprehension, vague delusions about men in her house, thinks her tea is poisoned. Died at 87 in Oxford Mental Hospital, bronchopneumonia and arteriosclerosis, especially in kidneys.

y 20. Parents live in new Council house in Dudley. Father a builder's labourer, strong and healthy, first cousin to his wife, an intelligent friendly woman.

Propositus 20. Male born 11.7.24. History. Mother felt unduly tired during pregnancy. Full time birth, not 7½ lbs. walked at 3½, speech defective, elementary school 4 years, occupation centre 5 years, Never ate much, liked milk puddings, always very constipated, urine had "strong unusual smell", no fits, no jaundice. Examination in Stoke Park at 15. Behaviour: Low grade imbecile, Merrill-Palmer 4.7 years, speaks few words, names and prints a few letters, feeds with spoon, clean habits, unduly easily afraid. Physical: Height 56 ins. Weight 67¾ lbs. Head 140: 178: 0.79. Very undeveloped, slight kyphosis, fair hair, blue eyes, slightly spastic gait, knee and ankle jerks very brisk, plantars flexor, numerous warts on hands, no nodules felt on nerves, blood W.R. negative. Urine positive.

.y 21. A family from rural Bedfordshire. Parents capable and intelligent, live in large clean village cottage. Father a farm labourer, has pulmonary tuberculosis and duodenal ulcer, first cousin once removed of his wife.

Propositus 21. Male born 1.2.28. History. Mother had uterine haemorrhage and hydramnios in 9th month. Born 3 weeks premature, always weakly, almost white hair; clean habits 1 year, walked at 5, chronic otitis media from age 4, huge appetite for raw meat, hated cake. Never at school, learnt a few words, liked music, no smell noticed. Examination in Stoke Park at 11 yrs. 5 mons. Behaviour: Idiot, Binet 19, Merrill-Palmer 2.4. Very quiet inactive placid, steady gait, defective habits. Physical: Height 52½ ins. Weight 59 lbs. Head 142: 178: 0.80. Fair hair, freckles and very bright pale blue eyes, good teeth, broad deep chest, prominent sternum and slight kyphosis. One dark large mole on leg. Blue cold hands. Knee and ankle jerks brisk, no clonus, plantars flexor. No nodules felt on nerves. Urine positive.

Sib. Female died 3 weeks, was "paralysed and deformed in her limbs", query phenylketonuric.

Maternal uncle, feeble minded, school until 14 but never earned living, childish, lacks ability, looks after poultry under supervision, urine negative.

ly 22. Parents slum dwellers at Hastings.

Propositus 22. Male born 11.1.29. History. Normal birth, never walked or talked, defective habits, occasional slight momentary seizures from infancy, would suddenly stare ahead for a few seconds, let his head fall, eruct wind and afterwards be distressed and whimpering, never unconscious. Examination in Stoke Park at 10 yrs. 6 mons. Behaviour: Low grade idiot, pays little attention, has to be fed, can now stand and walk a little, defective habits, washed thrice daily for offensive smell. Physical: Height 43 ins. Weight 50 lbs. Head 133: 170: 0.78. Bonny boy, moderate fair hair, china blue eyes, broad chest with kyphosis, tendon reflexes all brisk, plantars flexor. No nodules felt on nerves. Urine positive.

Sib. Male born 31.5.35. History. Weakly from birth, never sat up. Mother noticed that his urine and that of propositus had "strong smell which stings the eyes". Examination in Hastings Hospital at 4 yrs. 2 mons.

Behaviour: Idiot, happy smiling child, always the same, no screaming, no fits, no speech, incontinent, cannot stand, cannot drink from cup. Physical: Height 34½ ins. Weight 22 lbs. Well developed, pretty, red hair, dark blue eyes, no spasticity, tendon reflexes normal. Urine positive.

Sib. Male died 1 month; weak and wasted, query phenylketonuria.

Father 41. Psychopath. Unskilled labourer, poor intelligence, sadistic and pervert in intercourse with wife, always the same. Attends out patient mental clinic.

Father's father died 73. Gruff, disagreeable, hypochondriac in later years.

Female first cousin, 3 yrs. 3 mths. mongolian imbecile, Height 34¾ ins. Head 131: 155: 0.85. Fat, knock-kneed, blepharitis, urine negative.

y 23. Father has pleasant modern Council house, with well kept garden, in Gloucester.

Propositus 23. Male born 1.2.24. History. Mother had persistent vomiting during pregnancy, born at 8th month, weakling from birth, walked at 5, talked at 7, never at school. Examination in Stoke Park at 15 yrs. 5 mths. Very quiet imbecile, Merrill-Palmer 4.1. No speech, understands a little, clean habits, no smell noticed. Physical: Height 54 ins. Weight 65 lbs. Head 145: 189: 0.77. Very fair hair and pale blue eyes, freckles, some warts especially on hands, cafe au lait area on leg 3 ins. long. Flat depressed sternum, undescended testicles, tuberculous glands in neck, tendon reflexes normal, plantars flexor. Urine positive.

Sib. Female 14, imbecile, not examined. Urine positive.

Father 44, artizan. Mild depressive psychosis since death of wife a year ago. Deep but not constant sadness for a year, getting worse, lives alone, shuns company, has felt unable to work for years, sleepless, eats little, overwhelmed by tragedy of his life, afraid of and unable to plan for the future. Much insight.

Father's father died 64. Epileptic psychosis. Fits began at age 12. He grew slowly worse, more "queer", irritable, died in fit. His brother, an epileptic, died at 34 in mental hospital.

Father's mother 72. Overactive, overtalkative, untidy, frivolous and unduly happy. Senile hypomania, no intellectual decay.

ly 24. A family living in Cardiff; father an intelligent and capable small shop keeper.

Propositus 24. Female born 1902. History. Few facts known, always helpless idiot, no fits. Examination in P.A.I. Cardiff at 37. Behaviour: Low grade helpless idiot, pale and ill, pays little attention even to flash of light, noisy and restless, unable to feed herself, defective habits. Physical: Height 56¼ ins. Weight 76½ lbs. Head 145: 168: 0.86. Broad chest, kyphosis with depressed sternum, walks unsteadily on broad base, usually in bed, legs small and wasted, knee and ankle jerks brisk, plantars flexor, moderate fair hair, blue grey eyes, thyroid normal, menstruates irregularly, no smell noticed, no nodules felt on nerves. Urine positive.

Mother died 60 years. Hyperthyroidism during a few years. For last two years she was very thin and weak, had marked thyroid swelling, no exophthalmos, not emotional or excitable.

Maternal grandmother died 66. An invalid from the menopause, indefinite mental symptoms, extreme inactivity, often in bed half the year, not sad, no delusions.

y 25. Mother comes from large family of farm labourers in Rutlandshire; patient illegitimate, father unknown, but not a blood relative.

Propositus 25. Male born 4.4.18. History. Normal pregnancy and full time birth, a strong infant, walked at 2, spoke a few words only, no fits. Examination in Stoke Park at 21. Behaviour: Idiot I.Q. 14. Timid and easily frightened, no smell noticed. Physical: Height 63½ ins. Weight 85 lbs. Head 133: 184: 0.72. General underdevelopment, kyphosis with depressed sternum, very fair hair, blue eyes, marked exaggeration of all tendon reflexes, no spasticity, plantars flexor, thyroid and genitals normal. Urine positive.

ly 26. A Welsh and Irish family from the lowest social strata in the slums of Cardiff docks.

Propositus 26. Male born 5.10.04. History. A healthy infant, no fits, very backward at school, never held a job, used to wander and get lost. Examination in P.A.I. Cardiff at 35. Behaviour: Feeble minded, Binet 7 years, placid and happy, does simple tasks in institution, cannot read, can print a few words, no smell noticed. Physical: Weight 136 lbs. Head 152: 200: 0.76. Occasional tic of right eyebrow and lid. Fair hair, green-blue eyes, wide spaced incisors, very many minute raised spots on trunk, healed tuberculous left chest, cold abcess right ankle, tendon reflexes normal. Urine positive.

Sib. Female born 30.8.98. History. Healthy infancy but very backward at school, no fits. Examination in her home at 41. Behaviour: Feeble minded, Binet about 7½ years, Burt's Words Test 10.9 years. Placid, shy, suggestible, goes alone from home to a relative's shop, where she washes dishes and cleans floors. Physical: Short stature, very fat, no definite hypothyroidism, menses normal, fair hair, many hairy warts on face and neck. No nodules on nerves. Tendon reflexes normal. Urine positive.

Father, examined at 75. Bad tempered, slovenly, chronic alcoholic, unskilled labourer, somewhat dull intellect, said to have deteriorated since middle life.

ily 27. Father a shrimp fisherman in a Lancashire coastal village.

Propositus 27. Female born 16.6.19. History. Normal pregnancy and birth, defect noticed at 12 months, never spoke, occasional epileptic fits. Examination in Calderstones at 20. Behaviour: Idiot, no speech, defective habits, can feed herself, restless, often screams and kicks, curious jerky, fidgety voluntary movements of arms, legs and head. No epileptic fits for several years. Peculiar offensive smell from urine. Physical: Height 59 ins. Weight 110 lbs. Head 131: 172: 0.76. Short, broad chest with slight kyphosis, good nutrition, comely facies, steqdy gait, fair hair, blue eyes, thyroid normal, knee and ankle jerks exaggerated, plantars flexor. No nodules on nerves. Urine positive.

Two male sibs miscarried at 4th and 5th months.

ily 28. Parents in suburb of Manchester.

Propositus 28. Male born 20.2.31. History. Normal pregnancy and full time birth, severe eczema for years from 3 months old, no speech, walked at 4, liked to walk on toes from the start, always very excitable and easily frightened, three epileptic convulsions at 12 months, always severe constipation and strong smell in urine. Examination in Calderstones at 8 yrs. 3 mths. Idiot, insists on walking on toes, can say a few words, points to things he wants, hums tunes, cannot use spoon, frequent fidgety jerky little movements. Physical: Height 46¼ ins. Weight 42 lbs: Head 142: 170: 0.84. Bonny boy, fair red hair, pale blue eyes, fair complexion, internal strabismus left eye, wide spaced upper incisors, three small brown raised spots on trunk, unsteady gait usually on toes, tendon reflexes normal, thyroid and genitals normal. No nodules on nerves. Urine positive.

Father born 23.12. 05. Examined in home at 34. Anxiety states. Overconscientious, "high strung", hard working man, very efficient, history of duodenal ulcer, operation has been advised; increase of anxiety in recent months, vague head sensations, often sleepless and "tense".

Mother born 22.1.07. Examined in home at 32. Anxiety states. Chronic anxiety about herself, husband and work. Two anxiety attacks in past 10 years; felt faint, sick, very afraid. Violent crying attacks while looking after her idiot child. Sexual life with husband harmonious and satisfactory.

Maternal grandfather 55. Mild depression. Unduly sad and easily worried for a few years, insists on working

ly 29. Father a skilled manual worker, lives in suburb of Liverpool.

Propositus 29. Female born 9.9.25. History. Normal pregnancy and full time birth, defect noticed at 10 months, did not sit up or notice things, never spoke, walked at 4, craving for raw meat and fat, much vomiting of clear fluid in infancy, very weak, occasional petit mal, would suddenly stiffen and stare and tremble for a few seconds. Examination in Calderstones at 13 yrs. 8 mths. Behaviour: Restless noisy low grade idiot, many small fidgety movements, easily frightened, no speech, can feed herself, defective habits, no fits in hospital. Physical: Weight 108 lbs. Head 140: 178: 0.79. Well developed, broad chest, medium brown hair, brown eyes, thyroid normal, no menses, tendon reflexes exaggerated, plantars flexor, used to walk on toes, no smell noticed. No nodules felt on nerves. Urine positive.

ly 30. A large family in the slums of Warrington.

Propositus 30. Female born 15.3.09. History. Normal pregnancy and full time birth, large child, pretty, golden curls, gross defect soon noticed, no fits. Examination in Calderstones at 30. Behaviour: low grade idiot, pays almost no attention, does not recognise nurses, cannot feed herself, walks unsteadily, defective habits, inactive unless stimulated, kept on verandah because of very offensive smell, enjoys bumping head on wall, irregular menses often with apparent excessive pain. Physical: Height 56$\frac{3}{4}$ ins. Weight 122 lbs. Head 140; 184: 0.76. Short, broad, fat, coarse features, moderate fair hair, blue eyes, upper incisors and canines widely spaced, both feet small and soles quite flat, dry scaly skin, waxy pallor, much subcutaneous fat, thyroid not unduly small, possible myxoedema, obvious smell of phenylpyruvic acid, tendon reflexes normal, no nodules felt on nerves, urine positive.

Sib. Male, born Jan. 1911. History. Normal pregnancy,full time birth, defect soon noticed, never at school, no fits. Examination ~~AT-HOME~~ at home at 28. Behaviour: Idiot, I.Q. 18, no speech, understands a little, inactive, easily frightened, sits about grinning, clean habits, can wash and dress himself a little. Physical: Height 65$\frac{1}{2}$ ins. Head 142: 186: 0.76. Broad, well developed, muscular, coarse features, fair curly hair, blue eyes, tendon reflexes exaggerated, plantars flexor. Urine positive.

Sib. Male, born10. 11. 02. Examined at 37. Hyperthyroidism, duration unknown, exophthalmus, excessive perspiration, fine tremor of hands, pulse regular slow, no anxiety feelings.

Sib. Male, born 9. 11. 04. Examined. High grade feeble minded, not phenylketonuric. Stupid placid man, school standard 3 at 14 years.

Maternal grandmother, examined at 76 in Winwick Mental Hospital. She became insane at 47, and has spent most of her life since in mental hospitals; affective reaction type. At 76 she shows a senile deterioration, is frail, bedridden, arteriosclerotic,

shows diffuse and marked amnesias, particularly for recent events, with gross disorientation; stable composed mood, friendly, co-operative, comprehends well and answers at once.

nily 31. A part of family 30. Propositus 31 is maternal first cousin to propositus 30.

Propositus 31. Female, born 22. 7. 27. History. Normal pregnancy and full time birth, serious illness at 10 months, walked at 4 years, never spoke, no fits. Examination in Home for Defectives, Manchester, at 11 yrs. 10 mths. Behaviour: Idiot, no speech, understands a few simple commands, can feed herself, defective habits, no smell noticed, placid, not easily frightened, wanders aimlessly. Physical: Height 53¼ ins. Head 130: 177: 0.73. Broad stocky build, very broad chest bulging in front of clavicles, fair hair, blue grey eyes, wide spaced upper incisors, many small warts on arms and hands, thyroid and genitals normal, staggering gait, tendon reflexes normal, no nodules felt on nerves, no smell noticed, urine positive.

nily 32. Parents are pleasant labouring folk in dirty slum house in small Lancashire town.

Propositus 32. Male, born 25. 7. 19. History. Normal pregnancy, full time birth, gross defect soon noticed, no fits. Examination in Calderstones at 20. Behaviour: low grade idiot, no speech, eats only with fingers, defective habits, constantly sucking fingers, and making himself vomit by tickling throat, noisy, angry, restless, thin, dehydrated, ill. Physical: Head 136: 177: 0.77. Small and thin, poorly developed, very fair hair, blue eyes, circulation defective and feet blue and cold, inco-ordinate vision, tendon reflexes normal, plantars flexor, minute nodules can be felt in some intercostal spaces, possibly on the intercostal nerves, no smell noticed, urine positive.

Sib; Female, born 27. 10. 08. An idiot, no speech, destructive, restless, noisy, defective habits. Admitted to Lancaster Mental Hospital age 13, Height 52½ ins. Weight 66 lbs. Mitral systolic murmur, knee jerks exaggerated, plantars flexor. Had one fit at 2 yrs. and died at 27 after 8 epileptic fits. Probable phenylketonuria.

Sib. Female, born 3. 3. 09. An idiot, no speech, one fit at eleven months. Admitted to Lancaster Mental Hospital aged 9 yrs. 2 mths., Height 41½ ins. Weight 33 lbs. Restless, noisy, screaming, often makes peculiar movements with hands, peculiar rocking gait, flicking fingers, no understanding, defective habits, died at 23 of bronchopneumonia, probable phenylketonuric.

ily 33. A cheerful family in a Wigan slum.

Propositus 33. Male, born 8. 3. 25. History. Poor health in infancy, very retarded development, no fits. Examination in Calderstones at 14 yrs. 2 mths. Behaviour: idiot, no speech,

can feed himself, noisy, restless, jumpy and jerky in movement and easily frightened, nurses complain of his offensive smell, like garlic. Physical: Height 52 ins. Weight 66 lbs. Head 138: 182: 0.76. Pleasant featured boy, good nutrition, broad deep chest with slight kyphosis, fair hair and blue eyes, upper and lower incisor teeth widely separated, thyroid definitely uniformly enlarged, no tremor, no undue sweating, no exophthalmos, tendon reflexes all exaggerated, legs slightly spastic, plantars flexor, no nodules felt on nerves, urine positive.

Sib, female, born 2. 12. 22. History. Normal pregnancy and full time birth, defective, but not so backward as P.33. Special school until 14, since then kept at home, helps mother a little in house, docile, lazy, stable mood, little trouble to look after. Examination. at home, at 17. Behaviour: imbecile, Binet 4 years, timid, often over-eats. Physical: Height 59½ ins. Head 131: 181: 0.72. Small for her age, but well proportioned, pleasant features, fair hair, blue eyes, tendon reflexes all exaggerated, plantars flexor, menses normal, no nodules felt on nerves, urine positive.

ly 34. Father a skilled labourer in Lancashire town.

Propositus 34. Male, born 26. 8. 23. History. Normal pregnancy and full time birth, never talked, walked at 3, clean in habits at 3, frequent slight fits began at 3½, he would fall on the road for no obvious reason, but pick himself up at once, while sitting at table he would fall forward and bump chin, and look queer for a few seconds. He would often laugh before these attacks. Examination in Calderstones at 16. Behaviour: rather helpless idiot, can feed himself only with fingers, often defective in habits, screaming fits, unduly easily frightened, nurses sometimes notice a " curious and offensive smell ", no fits in hospital. Physical: Weight 81 lbs. Head 142: 185: 0.77. Broad and short, broad deep chest, prominent below clavicles, fair auburn hair, blue eyes, lower incisors widely spaced, upper crowded, tendon reflexes unduly easy to elicit, plantars flexor, a few moles and freckles on trunk, no nodules felt on nerves, urine positive.

Sib. Male, born 25. 5. 27. History. Normal pregnancy and full time birth, never walked or talked, yet mother thinks he was not as dull as P.34, and understood speech slightly, very severe constipation from infancy often requiring enemata, urine had " strong ammoniacal smell ", major epileptic fits began with teething, in batches at first every 2 or 3 months, slowly increasing. Admitted to Swinton Homes, Manchester, at 10, deeply jaundiced but soon improved on diet. Examination in Swinton Home at 12 yrs. 0 mths. Behaviour: helpless idiot, no speech, no understanding, cannot feed himself but reaches towards food, unable to walk, defective habits, stools have offensive smell quite different from those of other children, very severe epileptic fits, about every month, often expected to die. Physical: Head 131: 174: 0.75. Well developed good looking boy, can sit up, fair hair, dark brown eyes, well formed widely spaced incisors, dry scaly dermatitis, one small wrinkled reddish papilloma on left forearm, genitals and testes small, tendon reflexes in arms normal, knee and ankle exaggerated, double extensor plantar reflexes, markedly spastic legs, no nodules felt on nerves, urine positive.

Paternal grandmother, 82. In recent years memory for recent events and powers of retention have failed markedly. She remembers the past well, but repeats questions every few minutes. Able to walk about house.

35. Father a capable artisan in small Lancashire town.

Propositus 35. Female, born 29. 10. 12. History. Mother had definite lack of well being throughout pregnancy, birth normal, very fat infant, walked late, never spoke, slight "teething" fits from 12 months to 3 years, and frequent major epileptic fits from 9 to 10 years, often in sleep, always ravenous appetite and severe constipation, urine caused dermatitis on legs very easily, no smell noticed. Examination in Calderstones at 27. Behaviour: an inactive idiot, but very easily frightened, no speech, habits clean with care, can feed herself. Physical: Height 61½ ins. Weight 138 lbs. Head 140: 181: 0.77. short and fat, marked kyphosis with broad chest, fair hair and blue eyes, many spots of leucoderma, small wart-like structure on left cheek, menses regular, knee and ankle jerks exaggerated, plantars flexor, no nodules felt on nerves, urine positive.

Sib. Male, born 14. 7. 21. History. Normal pregnancy and full time birth, appeared a healthy infant, left school at 14 from standard 4, learnt little, never held a job, now washes cars in family garage, gives wrong change at petrol pumps, indolent, quiet, amenable, unadventurous, easily managed at home, no fits. Examination, at home at 18. Behaviour: Feeble-minded grade, Binet about 8 years, Burt's Words Test 5 years, Physical: Head 139: 186: 0.75. Well developed short stocky boy, good nutrition, no bodily abnormalities, fair hair, blue eyes, urine positive.

y 36. Parents live in new Council house in Barrow-in-Furness.

Propositus 36. Male, born 12. 6. 11. History. Normal pregnancy and full time birth, a very large infant, a few convulsions during teething, helpless idiot, required everything done for him until about age 10. Examination in Calderstones at 28. Behaviour: idiot, no speech, feeds himself with spoon, an excessive eater, very easily excited, infrequent epileptic fits, nurses recognise the unusual smell from urine, defective habits, Physical: Height 63½ ins. Weight 130 lbs. Head 141: 184: 0.77. Short and broad, good nutrition, fair hair, widely spaced upper incisors, light small pedunculated wrinkled skin tumours on trunk, broad chest, no kyphosis, genitals normal, small nodules can be felt on both great auricular nerves. Urine positive.

Sib. Female, born August 1924. History. Normal pregnancy and full time birth, many major epileptic fits up to age 2 and minor fits in which mouth would twitch a little, extreme constipation from infancy onwards requiring enemata, looked after by mother at home. Examination in her home at 15. Behaviour: low grade idiot, very easily frightened, unable to walk without support, cannot use a spoon, no speech, yet understands a few words, recognises mother, dribbling incontinence of urine, smell of phenylketonuria obvious, menses began at 13, often miss a month,

Physical: Height 53¼ ins. Head 143: 181: 0.79. Short and broad, comely facies, internal strabismus of right eye, fair hair, pale brown eyes, several large moles and small wrinkled skin-coloured "warts", broad chest with moderate kyphosis, fat, thyroid not felt but no signs of myxoedema, all tendon reflexes markedly exaggerated, double extensor plantar responses, slightly spastic legs, no nodules felt on nerves, urine positive.

ly 37. Parents live in squalor in filthy dilapidated slum house in Manchester.

Propositus 37. Male, born 6.4.21. History. Normal pregnancy and full time birth, walked at 4, never spoke, one epileptic fit at age 6 and another at age 14, always very constipated, peculiar "strong" smell of urine noticed. Examination in Calderstones at 18. Behaviour: helpless idiot, no speech, can walk and run, but not feed himself, very easily frightened, noisy and gluttonous. Physical: Height 59 ins. Weight 76 lbs. Head 143: 180: 0.79. Fair hair and blue eyes, notched irregular poorly formed incisor teeth, some psoriasis, thyroid definitely enlarged, fine tremor of outstretched hands, but good nutrition, no undue sweat, pulse slow, feet in talipes position, tendon reflexes normal, urine positive.

Sib. Male born 9.1.20. History. Normal pregnancy and full time birth, no fits, walked ay 2½ and said some words at 3, kept at home, little trouble. Examination at home at 19. Behaviour: imbecile grade, Binet about age 3, can say a few words, understands more, cannot read letters, clean in habits, requires help to dress and to lace his boots, does nothing, very fearful and easily frightened, afraid to go out much. Physical: Height 61 ins. Head 142: 181: 0.78. Pleasant facies, fair curly hair, blue eyes, incisor teeth wide spaced and notched, all tendon reflexes unduly brisk, no obvious thyroid disturbance, urine positive.

ly 38. A scattered family from Manchester slums, difficult to trace.

Propositus 38. Male born 23.11.91. History. Early history unknown. He had worked as a hospital porter and also spent 157 days in the Army. Following numerous court convictions for indecent assault, stealing, drunk, disorderly, embezzlement, false pretences etc. between ages 15 and 25, he was diagnosed as a feeble minded epileptic and spent some years in an epileptic colony and a mental hospital. Binet mental age 7 years at age 36. Three epileptic fits during 36th year, none since. Examination in Calderstones at 48. Behaviour: imbecile, Binet score 4 yrs. 10 mths, with scatter from 4 to 7 years, quiet and placid, does a little work stuffing mattresses, can read a few words of 2 or 3 letters. Physical: Height 63¾ ins. Weight 113½ lbs. Head 151: 185: 0.82. Quite well developed, thin, slight kyphosis, narrow grooved palate, two raised wrinkled pink skin nodules, 4 mm diameter, in right axilla and over left scapula, pupils slightly irregular, right smaller than left, react well to light and accommodation, constant involuntary rotatory tremor of right arm and hand, increased by stretching arm out, decreased on voluntary movement. He sits holding right hand in left. No loss of pain sense in arms and legs, all tendon reflexes brisk but normal, right knee jerk definitely greater than left, no clonus, plantars flexor, no muscular weakness, double flat foot, no nodules felt on

nerves, no abnormal smell noticed, urine positive.

Paternal uncle, 70, examined. A dullard, dull stupid dirty unskilled labourer with narrow mental horizon.

ly 39. A family of labourers in slum dwellings in industrial Widnes.

Propositus 39. Female born 26.11.19. History. Normal pregnancy and full time birth, walked at 5 years, talked little, vague history of serious illness for some years in childhood following serious injury to head, no fits, never at school. Examination in Calderstones at 20. Behaviour: low grade imbecile, Binet mental age $3\frac{1}{2}$ years, little speech, can feed herself, has to be washed and dressed, incapable of work, habits sometimes defective, irritable and quarrelsome, easily excited, abnormal smell noticed. Physical: Height 61 ins. Weight 137 lbs. Broad and short, fair hair and blue eyes, tendon reflexes all exaggerated, plantars flexor, irregular menses, no nodules felt on nerves, urine positive.

Sib. Female born 29.7.07. History. Normal pregnancy and full time birth, no fits, walked and talked late but went to school from 5 to 7, then had ? pneumonia and meningitis and remained at home. Examination in Calderstones at 32. Behaviour: imbecile grade, Binet $6\frac{1}{2}$ years, does some cleaning work in institution, often excitable, clean in habits, moderate speech, no smell noticed. Physical: Height 64 ins. Weight 129 lbs. Broad and well nourished, fair hair, blue eyes, all tendon reflexes exaggerated, plantars flexor, no nodules felt on nerves, urine positive.

Sib. Male born 26.7.21. History. Normal pregnancy, full time birth, very ill at 2 months, no fits, never spoke, walked at about 12. Examination in Calderstones at 18. Behaviour: idiot, Binet 3 years, no speech but understands a little, can polish floors, often excitable, habits sometimes defective. Physical: Height $66\frac{5}{4}$ ins. Weight 144 lbs. Well developed and broad, fair hair and blue eyes, large clumsy hands, small genitals, deficient growth of hair on chin, no nodules felt on nerves, no smell noticed, urine positive.

Half Sib. Male born 23.4.00. Examination at his home age 39. Hypochondriacal religiose epileptic, average intelligence, steel worker at Widnes. The blood groups of this man, his mother, and her other children prove that he must be a half-sib.

ily 40. A Manchester family.

Propositus 40. Female born 26.10.15. History. Early history unknown, admitted to Calderstones aged 7, an epileptic idiot. Examination in Calderstones at 24. Behaviour: idiot, no speech, hums tunes, can feed herself a little, defective habits, can walk and run easily, habit of twitching the hands and face in irregular voluntary movements, always frightened, occasional severe major epileptic fits about 2 a month with much vomiting after the seizure, 6 fits during 16th year, 4 fits in 17th, 7 fits in 18th year. Physical: Height 47 ins. Weight 105 lbs. Head 141: 182: 0.77. Very short, stocky, muscular, good nutrition, fair hair, pale blue eyes, good teeth, two small brownish raised spots on trunk and two on face, menses normal, no nodules felt on nerves, no smell noticed, arm reflexes normal, knee and ankle jerks exaggerated, plantars flexor, urine positive.

Sib. Female born 1931. History. Early history unknown, admitted to Calderstones aged 7. Examination in Calderstones at 8. Behaviour: idiot, no speech, able to walk but unsteady when runs, has to be fed, clean under supervision, no smell noticed, quiet, inactive, apprehensive and easily frightened, occasional jerky voluntary twitching of hands and head, no fits, Physical: Height 44½ ins. Weight 58 lbs. Head 140: 173: 0.81. Quite well developed, broad, comely facies, fair hair, dark blue eyes, good teeth, knee and ankle jerks exaggerated, plantars flexor, arm reflexes normal, no nodules felt on nerves, urine positive.

Sib. Female died at 12 months, never normal, could not walk or talk, probably phenylketonuric.

ly 41. A large family in the slums of Manchester.

Propositus 41. Female born 23.12.14. History. Normal pregnancy and full time birth, a weakly infant, always very constipated, never spoke, began to walk at 4, fed herself at 6, no fits. Examination in Calderstones at 25. Behaviour: idiot, I.Q. 6, no speech, restless, noisy, often wailing, rarely experiences fear, often throws head and arms about in voluntary jerky almost twitching movements, can feed herself, incontinent, peculiar offensive smell from urine, no menses. Physical: Height 57½ ins. Weight 112 lbs. Head 135: 189: 0.71. Short and broad, coarse featured, asymmetrical face, fair auburn hair, blue eyes, no kyphosis, three wart-like spots on trunk, many leucoderma spots on legs, tendon reflexes present, plantars flexor, no nodules felt on nerves, skin dry, can hyperextend fingers, soles of feet quite flat. Urine positive.

Sib. Female died 5, bronchitis, an idiot, never walked or talked, had one epileptic fit, probable phenylketonuric.

Sib. Female died 11, an idiot, never spoke, no fits, probable phenylketonuric.

.ly 42. A Liverpool family with monovular twins, phenylketonuric.

Propositus 42. Male born 6.5.23. History. Few facts known, said to have had a few epileptic fits. Examination in Calderstones at 16. Behaviour: idiot, I.Q. 10. No speech, cannot use spoon, incontinent of bladder and bowel, peculiar offensive smell noticed in urine, always noisy, restless, tears clothes, easily frightened. Physical: Height 62 ins. (on toes), Weight 92 lbs. Head 140: 185: 0.76. Short, broad, well nourished, pleasant featured boy, see photographs, fair hair, broad chest with slight kyphosis, widely separated upper incisor teeth, several warts on hands, several moles on trunk, also many darkish pigmented spots and small white patches of leucoderma, thyroid and genitals normal, for years has walked only on toes, no spasticity in legs, tendon reflexes normal, plantars flexor, no nodules felt on nerves. Urine positive.

Sib. Male born 6.5.25, probable monovular twin. History. Few facts known, no history of fits. Examination in Calderstones at 16. Behaviour: idiot, I.Q. 10. No speech, excessive and rapid eater, can use spoon, incontinent of bladder and bowel,

offensive smell noticed in urine, noisy, restless, bites himself and pokes eyes. Physical: Height 62 ins. (on toes), Weight 79 lbs. Head 134: 186: 0.72. Short boy, see photograph, fair hair, incisor teeth widely separated, broad chest with slight kyphosis, thyroid and genitals normal, always walks on toes, steady gait, some contracture of achilles tendon, no spasticity, tendon reflexes normal, plantars flexor, no nodules felt on nerves, urine positive.

Father 41, examined. Psychopath; unsociable unreliable man, takes extreme opinions, unfaithful to three wives, never long in one job.

Maternal first cousins. Females, idiots. One died at 17, a helpless idiot, could not walk or talk; the other died at 7, could walk and say a few words, but very backward; type unknown.

ly 43. A Lancashire family showing insanity and three cases of phenylketonuria.

Propositus 43. Female born 17.3.01. History. Normal pregnancy and full time birth, a strong infant, few illnesses, walked at 5, never spoke, could understand speech and messages to shops, tuberculous disease of right shoulder began at 17, no fits. Examination in Brockhall at 38. Behaviour: imbecile, I.Q. about 21, lethargic and placid, understands a few words, but has no speech, can feed herself, but not dress, huge appetite, occasionally defective in habits, menses regular. No smell noticed. Physical: Height 58 ins. Weight 102½ lbs. Head 140: 178: 0.79. Broad and fat, coarse featured, moderate fair hair, blue eyes, teeth crowded, dry skin but no definite hypothyroidism, ungainly gait with slight kyphosis, tendon reflexes normal, plantars flexor, no nodules felt on nerves, partial tuberculous ankylosis of right shoulder with healed sinuses. Urine positive.

Sib. Male born Nov: 1906. History Born defective, walked early but talked late, at school until 14 but learnt little, never earned living but does odd jobs at home, carries coal, cleans floors and windows. Had 3 major epileptic fits between ages 17 and 19. Always quiet, amenable, timid, hates going out. Examination at home at 33. Behaviiour: Imbecile, I.Q. 40, understands simple commands, very little speech, sits grinning. Physical: Height 68¼ ins. Head 150: 192: 0.78. Thin, asthenic habitus, kyphosis with depressed sternum, moderate fair hair, tendon reflexes exaggerated, plantars flexor, slight tremor of hands, much perspiration, small nodules palpable on great auricular nerves. Urine positive.

Sib. Female born 27.11.15. History. Born defective, late in walking, little schooling, no fits, always very constipated, very easily excited and upset by company. Examination at home at 24. Behaviour: Imbecile, I.Q. 43, has little speech but understands more, clean habits, can wash and dress herself, helps a little in house, rather higher grade than sib male 33. Physical: Height 59½ ins. Head 139: 185: 0.75. Broad chest with slight kyphosis, fair hair and blue eyes, narrow pointed tongue and projecting incisors, thyroid unduly full, but no tremors or rapid pulse, unduly jumpy and jerky in movement, all tendon reflexes markedly exaggerated, plantars flexor, nodules felt on right auricular nerve. Menses regular. Urine positive.

Father died 59. Mild paranoid psychosis. Always alcoholic, became suspicious and queer after 50, thinking people at home and at work were against him, afraid of acting on his suspicions, easily angered.

Maternal aunt, 72, examined. Imbecile, not phenylketonuric. Placid, inactive, kept at home, very little speech, can wash and dress, very short stature.

Maternal grandfather, died 63, psychopath. Always violent-tempered, alcoholic, deserted his family.

Mother's father's mother, senile psychosis, became very childlike in old age. Her brother went insane in middle life.

ily 44. A family in slums of Liverpool.

Propositus 44. Male born 30.1.11. History. Normal pregnancy, full time birth, born in membranes, placenta said to be abnormal. Soon clean in habits, walked at 2, at school from 5 to 14, but learnt nothing, unduly easily frightened, no fits. Examination in Brockhall at 28. Behaviour: Imbecile, I.Q. 25, understands a little speech, can say a few sentences in slurred speech, clean in habits, can wash and feed himself and dress himself except for collar and tie, not now easily frightened. Physical: Height 66¼ ins. Weight 117 lbs. Head 139: 188: 0.74. Well developed, comely, very fair hair, blue eyes, broad chest with kyphosis, high palate, tendon reflexes all exaggerated, plantars flexor. Urine positive.

Sib. Female died 3 years, pneumonia. Idiot, very backward in talking, could not run, no fits, probable phenylketonuric.

ily 45. Propositus and brother are illegitimate twins; relatives unknown.

Propositus 45. Female born 17.10.08. History. Unknown; was at school for some years. Examination in Brockhall at 31. Behaviour: Feeble minded grade, Binet 8½ years, Porteus Maze 6½ years. Clean and tidy in habits, does some cleaning work, emotionally unstable, retiring, inactive, very easily frightened, menses normal. Physical: Height 58¾ ins. Weight 125 lbs. Head 142: 179: 0.79. Well developed but short, comely, moderate fair hair, blue eyes, chronic irritative dermatitis of obscure cause, tendon reflexes all exaggerated, plantars flexor, perspires very easily. Urine positive.

ily 46. A London family with four affected children.

Propositus 46. Female born 19.8.31. History. Normal pregnancy and full time birth. The most severely affected of four defective children, walked at 3, never spoke, infrequent major and minor epileptic fits at irregular intervals from age 9 months; always very constipated. Examination at Stoke Park at 7 yrs. 11 mths. Behaviour: Low grade idiot, cannot walk unaided, no speech, incontinent, no smell noticed, pays little attention, bites and screams. Physical: Height 47 ins. Weight 51½ lbs. Head 127: 182: 0.70.

Well nourished, bonny, fair whitish hair, dark blue eyes, knee and ankle jerks greatly increased, plantars flexor, urine positive.

Sib. Male born 25.11.18. History. Normal pregnancy and full time birth, developed late, curious craving for oranges, no fits. Examination in Stoke Park at 21. Behaviour: Imbecile grade, I.Q. 34, quiet, placid, moderate amount of speech, characteristic smell from urine. Physical: Height 67½ ins. Weight 115 lbs. Head 143: 200: 0.71. Tall, well developed, comely, very fair golden hair, pale blue eyes, a few freckles on face and forearm, notched, poorly formed teeth, thyroid and genitals normal, tendon reflexes normal, plantars flexor, no nodules felt on nerves, urine positive.

Sib. Female born 3.2.26. History. Normal pregnancy, full time birth, walked and talked by 2 years, at school, parents do not think her abnormal. Examination at home at 13 yrs. 5 mths. Behaviour: placid, looks stupid but answers quickly, Binet age 8 yrs. 10 mths, I.Q. 70, Burt's Words Test 12.8 years. Physical: Height 66½ ins. Head 135: 195: 0.69. Well developed, very fair hair, dark blue eyes, many freckles, tendon reflexes normal, menses not begun, urine strong positive.

Sib. Male born 4.6.29. History. Normal pregnancy and full time birth; rather late in walking and talking, parents think him "dull and stupid", backward at school, no fits. Examination at home at 10 yrs. 1 mth. Behaviour: Feeble minded grade, Binet age 5 yrs. 4 mths. I.Q. 50, can read no words; cheerful obedient boy. Physical: Height 55¾ ins. Head 135: 181: 0.75. Short but broad, very fair hair, poorly developed and notched incisors, tendon reflexes normal. No nodules felt on nerves. Urine positive.

Appendix III

Record of Distant Relatives

including grandparents, uncles and aunts, first cousins, half sibs and some more distant relatives.

Unless otherwise stated, relationship is given as relationship to the propositus. F denotes Father; M, Mother; FF, Father's Father; FM, Father's Mother etc: m denotes male; f, female; ch, children; d, died; d.i., died in infancy. Age is given in years after the letter indicating sex, thus f2 means female aged 2 years: 2f means two females. The race to which the grandparents belong, and the part of the country in which they were born, are recorded where they are known.

(These records are more easily consulted together with the family charts in appendix IV.)

mily I. FF English Suffolk d 83 paranoid. FM English well d 72.
F's sibs: m d i : f paranoid : m 62 well (ch: several well) :
m 57 well (ch: several well): m 56 well (ch: several well): 3 m d i.
MF English Kent well d 52. MM English Suffolk well d 72.
M's sibs: m well d 17 : M : m adult well (ch: 3 f well) :
f adult well (ch: 2 m adult, m in teens all well).

mily 2. FF English unknown. FM English rural Essex d 77 psychosis.
F is illegitimate, is first cousin to M. (FM sib to MF)
MF English d 83 psychosis. MM well d 74.
M's sibs: order uncertain. m d 54 psychosis: f adult well: f adult
well (ch: f, 4 m all well): f welldadult: 3 m well d adult.

mily 2 a. FF English well d old. FM well d old. MF well d old. MM well d old.
F's sibs unknown. F is first cousin to M (FM sib to MF)
M is the FM of propositus in family 2. M's sibs: m adult well (ch:
2 f well): f adult well: f well d adult (ch: several well) :
f adult well (ch: m, f well): M: m (MF in family 2) d 83 psychosis
(ch: see M's sibs in family 2): m adult well (ch: 2 f well d adult):
m adult well: m adult well (ch: 3 f, 3 m well): m adult well (ch: f
adult well)

mily 3. FF English rural Essex well d 80. FM English 75 well.
F's sibs: F: f adult well (ch: 2 f, m well) : m adult well (ch: 2 f,
m at school well): m adult well (ch: m, f well): f well (ch: 2 m, f
well): m adult well(ch: m well): f adult well (ch: m well):
m adult well.
MF English well d 69. MM English well d 35 childbirth.
M's sibs: M: f adult well (ch: 4 f, m well): m adult well (ch: f
well): f adult well (ch: 3 m, 2 f well): child d i.

mily 4. FF English Cornish d 59 psychosis. FM English Cornish well d old.
F's sibs: f well d 50 to 60: m chronic alcoholic d 55 (ch: f well
adult): 3 adult males unknown: f d i : F psychopath: f 69 well
(ch: 3 m, 3 f well).
MF English Londoner well d 62. MF's sibs: m well d 81: f well d 77:
MF: m 76 well. MFF well d 70. MFM well d 96.
MM 72 hypomania. MM's sibs: MM: f 70 well: m well d 55.
MMF English Londoner. MMM English Norfolk well d 80.
M's sibs: m 55 well: M: f d i : m 45 well (ch: ⅓ m, 4 well):
m 43 well: m 42 well: m well d 42 Tb (ch: f 16, m 12 well): m 40 well:
m d 4 mons: m well killed war 19: f 36 well: m 33 well (ch: f 6,
m 1 well).

mily 5. F. French Huguenot descent, well d 77.
M. French Huguenot descent, well d 77
Further facts not known.

ily 6. FF English Cambridgeshire well d old. FM English well d 80.
F's sibs: F: m well d adult accident (ch: 6 well): f 65 well (ch: m adult well): f adult well (ch: m well, m d i)
MF English well d young adult. MM English well d 65.
M's sibs: order unknown. f 70 to 80 well: f d young adult: 2 m adult unknown

ily 7. Parents unknown, English probably Cornish. Further facts not known.

ily 8. F English, an only child. His parents unknown.
MF English 78 well. MM well d 41.
M's sibs: m d 4: m psychopath
Half sibs: f 30 well (ch: 3 m well): f 29 well: f 28 well: m 26 well: f 24 well: f 12 well: f 11 well.

ily 9. FF Scot Aberdeen 60 well. FM Scot 58 well.
F's sibs: m 37 well (ch: m 11, m 10, m 7 well): f 36 well: F: f 30 well: f 29 well: m 27 well (ch: f 3, f 2 well): m 25 well (ch: f 2 well): m 16 well: f 15 well.
MF Scot Aberdeen 67 well. MM Scot 62 well.
M's sibs: m 39 well (ch: m 17, f 13 well): m 37 well (ch: f 12, f 11, f 7, m 1 well): m 32 well (ch: f 7, f 4 well, f d 2 pneumonia): f 22 well: f 19 well.

ily 10. FF Scot, Sutherlandshire well d 78. FM Scot well d 78.
F's sibs: F: m 69 well: f 64 well.
MF Scot well d 71. MM Scot well d 85.
M's sibs: m well d 45: M: m well d 62: f 62 well: m 60 well: f well d 50: f 56 well.

ily 11. FF Scot Stirlingshire well d 70. FM Scot chronic anxiety d 48.
FMM well d old (sib to MM)
F's sibs: F anxiety states: m 54 depression: f psychosis d 46, married her first cousin (ch: m 29, f 27 both well, f normal d 7, f 22 well, m 18 feeble minded): m 49 hyperthyroidism (ch: f 16, m 12 both well, stillbirth, f d 1 accident): f d 46 exophthalmic goitre (ch: 2 m, 2 f well ages 10 to 23): f d 28 exophthalmic goitre: m 35 anxious hypochondriac (ch: 2 f ages 2 and 1 year well).
MF North Irish well d 83. MM well d 55.
M's sibs: order uncertain: m 65 well (ch: f 21 well): m 63 well (ch: m 30, m 28, m 26, m 20 well): f 55 well (ch: m 26, f 23, m 21, f 19, f 15 all well): f 53 well: m 50 well: f well d 29 Tb: m 48 well (ch: f 23, m 13, m 11, m 7 all well).

ily 12. FF Scot Shetland 86 well. FM well d 51.
F's sibs: m 60 well: m 60 twin well (ch: m 13 well): F: m 56 well (ch: f 28, m 26, f 23, m 20 all well): f 54 well (ch: f 18, m 14 well): m 52 well (ch: m 8 well): m 50 well: m well killed in war 28: m well killed in war 25: m 44 well: m killed in war 23: m 40 well.
MF Scot well d 80. MM d 61 diabetes
M's sibs: m well d 64 (ch: m 34, m 30, f 27 all well, f d 11 mons fits): f 64 well: f well d 60: f 60 well: f 58 well (ch: m well d 7, m 30 well, f 27 well, m 25 well, f 22 well): f well d 35(ch: f 30 well, f d 7 unknown, f 25 well): f d i : M.

ly 13. FF English Devon 60 well. FF's sibs: f adult well: f adult d accident: m imbecile: m 44 psychosis. FM English Devon 56 well, has 2 male sibs well.
F's sibs: order uncertain: f adult well (ch: 4 m adult well): f adult well (ch: 3 f, 2 m well): f adult well (ch: m, 2f well): m adult well: m adult well (ch: 2 miscarriages): m adult well: 4 sibs d i and 3 miscarriages.
MF English well killed in war 32, had 3 male sibs well. MM hypochondria.
M's sibs: m 33 anxiety neurosis (ch: f 9 well): m 23 psychopath: m adult well (ch: m well): m adult well (ch: f well): miscarriage at 3 months.

ly 14. FF English Devon 74 well. FM English Devon 71 well.
F's sibs: m well killed in war 24: f 46 well (ch: m 20, m 18, f 17 all well): F: m 44 anxiety neurosis (ch: m 12, f 13 well): m 36 well (ch: f 3 well): m 33 well (ch: f 2 well).
MF English well d adult. MM English 78 well.
M's sibs: m well killed in war: m well killed in war: m adult well (several adult children): m adult well (ch: m 4, f well): m adult well (ch: 2 m,3 f well): m adult well: f adult well (ch: 2 f well, f d 14 congenital heart): f adult well (ch: 3 m well): f adult well (ch: m,4f well): f adult well (ch: f 21 well, m well d 2): f adult well (ch: m, 2 f well): M.

ly 15. Propositus illegitimate and father unknown.
MF English Devon well d old. MM English Devon well d 56. Her Brother was a mental defective, probably imbecile.
M's sibs: f 40 anxiety neurosis (ch: f 13, f 10 well): M: f 36 well (ch: f well): m 35 feeble minded epileptic.
Half sibs: f 15 well: f well d 3 months pneumonia: m 10 well.

ly 16. FF English Devon 80 to 90 well. FM English Devon 80 to 90 well.
F's sibs: F: f adult well (ch: 2 m well): f adult well (ch: several well).
MF English Devon d psychotic. MM English Devon well d 68.
M's sibs: stillbirth: m adult well (ch: m, f adult well): m adult well (ch: 2 m adult, m 14, f adult well, f well d peritonitis): m adult drowned accident (ch: several well): M: m 47 well (Ch: f 17 imbecile not phenylketonuric, m well d 6 diphtheria, f 11 well).

ly 17. FF English Devon 80 to 90 well. FM English Devon well d sixties.
F's sibs: order and ages uncertain: 2 m adult well: m adult well (ch: several well): m well killed in war (ch: m, 2 f well): f adult well (ch: f well): f well d adult Tb: 3 m d i.
MF English Devon d psychotic about 37. MF's sibs: 3 f adult well: f 49 psychotic: m adult well (ch: several well).
MM English Devon (is the MM of propositus 16). She had 2 m and 3 f sibs well.
M's sibs: m well killed in war adult: f d i: twins d i: M

ily 18. FF English Somerset well d 40 to 50. FM English Somerset well d 40 to 50. F's sibs: f well d 70 (ch: several well): f well d 70 to 80 (ch: several well): f 78 well (ch: m d 60 muscular dystrophy, m d 30 muscular dystrophy, m 52 has muscular dystrophy, f d 30 influenza, m d 50 Tb, f d 40 muscular dystrophy, m 42 well, m 38 well, m 34 well, f 30 well, m d 3 months). Father and paternal uncle of these children had muscular dystrophy.
MF Welsh well d 5o to 60. MM Welsh well d 84.
M's sibs: m well killed in war (ch: several well): m adult well (ch: several well): m adult well (ch: several well: m well d adult: m adult well (ch: several well).

ily 19. FF English Gloucestershire 63 well, had 4 m, 5 f sibs well.
FM English Gloucestershire 62 well, had 4 m and f sibs well
F's sibs: f 40 well (ch: m 16 well): m 37 well (Ch: f 9, m 5 well): m twin d birth: F: m 30 well: m 27 well (ch: f 2 well): f twin 27 well (ch: m 4, f 3 well).
MF English Gloucestershire 75 well. MF's sibs: 3 m and f well: f senile psychosis d 87.
MM English Gloucestershire 73 well. MM's sibs: 3 f, 2 m well.
M's sibs: f well d 21 peritonitis: f 48 encephalitis lethargica, striatal rigidity (ch: f 24, m 21, f 19 well, f d 15 months, m d 12 months): f 46 well (ch: f, 2 m well): m 44 well: m 40 well (ch: 3 m, f well ages 13 to 6): m well killed in war 19: m 38 well (ch: f 9, f 8, f 5, f twins 2 well): stillbirth: M.

ily 20. FF English Industrial Warwickshire 66 well. FFF is MMF, well d 71: FFM is MMM, well d 73. FM English Industrial Warwickshire well d 42.
F's sibs: f d i: m well d 41 (ch: 2 m, 2 f ages 16 to 22 well): m 45 well (ch: 2 f, m ages 6 to 18 well, f well d young): m 43 well married first cousin (ch: m 16 well, m well d 6 months pneumonia, m 3½ well): F: f 39 well (ch: 5 m, 3 f ages 4 to 19 well): m 37 well (ch: m 8 well).
MF English Industrial Warwickshire paralysis agitans since 71, no mental change, d 73. MM English Industrial Warwickshire (sib to FF) well d 46.
M's sibs: m well d 2: m well d 42 war wounds: m 43 well (ch: 3 f, 2 m well): f 41 well (ch: 3 m, 3 f well): f 44 well married first cousin (ch: see above): M: m 31 well (ch: f 2 well).

ily 21. FF English rural Bedfordshire well d 80. FM English rural Bedfordshire (half sister to MF) well d 71, had 10 healthy sibs.
F's sibs: m well killed in war 40 (ch: m, 2 f well, m well d childhood scarlet fever): m 60 well (ch: m, 2 f well): f 59 well (ch: m well): m d i unknown: m d 4 unknown: f 54 well: m well killed in war 29: f 49 well (ch: m, 2 f well): f 47 well (ch: 3 m, f well): m d i unknown: F.
MFF is also FMF, state unknown d 90. FMM well d ?. MFM well d 80.
MF English rural Bedfordshire 67 well, had 6 brothers and 4 sisters all healthy. MM English rural Bedfordshire 57 well.
M's sibs: m 38 well (ch: 2 m well): M: f well: f well (ch 2 m, f well): f well: f well (ch: m well): m well (ch: m,f well): m feeble minded: m d i unknown: f 16 well.

ily 22. FF English Sussex hypochondriac d 73. FM English Sussex 68 diabetes mellitus.
F's sibs: f 50 to 60 well (ch: f d 5 weeks fits, f 18 well): f unknown (ch: f 18 well): m well: m d birth: F: f well: f well: m well killed 21 accident.
MF English Sussex 62 well. MF's sibs: m well d 50 to 60 (ch: f 32 well, m 30 well): m well d 29: m 65 well (ch: m d i, 2 f adult well, f well d 36): m well d youth: MF: f 58 well (ch: 7 m well, m d 7 unknown, f well): f adult well.
MM English Sussex 62 well. MMF 86 well. MMM well d 43 nephritis.
MM's sibs: MM: f 60 well: f 58 well: f 56 well (ch: m d 20 unknown): m 53 well: m well d adult: f 49 well: several died in infancy.
M's sibs: M: f 33 well (ch: f 3 mongol): f 28 well.
(The parents of the mongol are 3rd cousins, thus FFMF sib to MMFM)

ily 23. FF English rural Gloucestershire epileptic d 64. His brother insane epileptic d 34. FM English rural Staffordshire 72 hypomanic.
F's sibs: m d i: F: f d 5 months diarrhoea: f 37 well (ch: 2 m, f well): f 35 well (ch: m, f at school well).
MF English rural Wiltshire well d 77. MM English unknown d 45.
M's sibs: M is youngest, order of others unknown. m well (ch: several m well): m well (ch: 3 m, f well, in teens): m well (ch: 6 m well): m well killed in war: f well d 42 (ch: 2 f, 2 m well, f d unknown)

ily 24. Half sib m 5 well, urine negative. Step-mother 44 well.
FF English rural Devon well d 89. FM English Sussex well d middle age.
F's sibs: F: f 55 well, urine negative: child d few days:
MF English Gloucestershire well d 65 cerebral seizure.
MM English ? mental disorder d 66.
M's sibs: m d i: M: f well d 39: f 65 well (ch: f 37 well, has 6 children of whom one male is mentally defective and deformed in one arm, m 23 well): f 59 well, urine negative: m d 9 months: 4 children d i order unknown.

ily 25. Half sibs: f 19 well: f s.b.: f 15 well: m 12 well: m 7 well.
Step-father d 43 epilepsy, cause unknown.
MF 66 well, cousin to MM 63 well. All maternal ancestors are English from Rutland, Father was Welsh.
MF's sibs: 7 m all over 70 well: f 72 well, married first cousin (ch: f adult married, state unknown, said never to have menstruated: f d 13 unknown: m d 30 Tb: m well)
MFF well d 60. MFM well d old, was sib to MMMM well d 72.
MMMF well d 80 to 90. MMM well d 79. MMF well d 60.
MM's sibs: order unknown: some stillborn: m d 3 scarlet fever: f 69 well: m 60 well: m 56 well, twin sister d 2 weeks: m well d 66: f 46 well, married a cousin (ch: unknown).
M's sibs: M: f 42 well (ch: m,f well): f 39 well (ch: m, f well) m 36 well (ch: 4 m 3 in teens one 7, f one year, well): m 32 well (ch: f 4, m 2 well): f well (ch: 4 m, f eldest 9 years well): m well (ch: m 2 well): m well (ch: 2 f, m well): m well d 2 pneumonia: m 21 well.

mily 26. FF Irish d 45 to 50 unknown. FM Irish d 103 unknown.
F's sibs: 16. Ten unknown, 4 m well; m d 32 unknown: f d 40 unknown.
MF Welsh well d old. MM Welsh unknown.
M's sibs: m well d old: M.

mily 27. FF English Lancashire coast 70 slight seizure at 70.
FFF English Lancashire coast well drowned at 36.
FM English well d 49 influenza.
F's sibs: f 47 well (ch: m 25, m 24 well): F: m 43 well: m 41 well (ch: 2 m, 2 f ages 20 to 12 well): f 31 well.
MF English industrial Stafford well d 51. MM English well d 69.
M's sibs: m 50 to 60 well (ch: 2 m, f over 20 well): m well d 47 (ch: 3 m, f ages 22 to 16 well): Twins, probably monovular, f 45 well (ch: m 15, f 12 well), f d 39 ?pernicious anaemia (ch: m 12 well): f 46 well: M: f well: f well (ch: f in teens well): f well (ch: 4 f 13 and under well): f 33 well (ch: f in teens well).

mily 28. FF English Wiltshire 67 well. FM English Lancashire 62 well, eldest of 15 all well.
F's sibs: m 38 well (ch: m 5 well): F: f d 16 months unknown: m 29 well: m 28 well: m 25 well: f well d 2 yrs. 8 mons. influenza: m 21 well.
MF English Lancashire 55 depression. MM English 55 well.
M's sibs: Misc.: M: m 31 well: f 26 well (ch: f 1 well): m 22 well (ch: f 7 months well)

nily 29. FF English Lancashire well d 66. FM English Lancashire well d 62.
F's sibs: m 58 well: m 55 well (ch: 2 m, twin f in teens well): F: f 51 well: m well killed in war 29 (ch: m well): m well d 7: f 44 well: m 41 well: f 36 well (ch: 2 m ages 16 and 12 well): f 34 well.
MF English Lancashire 77 well. MM Scots 75 well, has 4 brothers well.
M's sibs: m 54 well (ch: f 30 well): m well d 1 yr. 7 mons. measles: m 50 well (ch: m 18, m 9, f 5 well): M: m well killed in war 24: f 43 well (ch: m 8 well): m 40 well.

nily 30. FF English industrial Lancashire well d 70. FM English industrial Lancashire well d 84.
F's sibs: m 67 well (ch: 2 f, 2 m well): F: m well (ch: 6 sex unknown well): m well (ch: 2 f well): f well (ch: 2 m, f well): f 38 well (ch: 3 m well, f d 12 unknown): 2 d i. order unknown.
MF English industrial Lancashire well d 65. MM English industrial Lancashire 76 insane.
M's sibs: f well d 56 (ch: twins died, 2 f adult well): M: m well (ch: 10 well sex unknown): m 46 (ch: 3 m well, f d 12 unknown): m well (ch: m 15, m 13, m 10, f 6 well): m well killed in war: f mother of propositus 31.

nily 31. FF English rural Cheshire 69 rheumatic cripple since 49.
FM English industrial Lancashire 61 well.
F's sibs: f 43 well (ch: f 18, f 8 well): f well (ch: f 18, m 16, f 14, m 12, m 9 all well): F: m 29 well (ch: m 3, m 1 well): f 25 well (ch: f 8, m 5, twin m and f age 1 well): m 21 well.
MF, MM, and M's sibs are those of propositus 30.

ily 32. FF English rural Lancashire well d 45. FM English rural Lancashire well d 50 to 60, perhaps a blood relative to FF.
F's sibs: m 61 well (ch: f well): f 59 well: f 57 well: F: m well d 52: m 51 well (ch: f well): f 49 well: f 47 well: m 43 well.
MF English Lancashire 79 well. MF's sibs: 4 m, 2 f well d old: f d $3\frac{1}{2}$ unknown: m twin to MF d 2 unknown.
MFF well d 70 to 80. MFM well d 70 to 80 seizure.
MM English Lancashire well d 76.
M's sibs: f d i unknown: m 60 well (ch: 2 m, 2 f well): M: m well d 53: f 50 to 60 well: m 47 well (ch: 2 m ages 20 and 18 well).

ily 33. FF English industrial Lancashire well d 49. FM English industrial Lancashire 71 well. FMF well killed accident adult. FMM well d old.
F's sibs: 2 d i sex unknown: f 49 well (ch: sb, f 17, m 15, f 10 well): F: f 40 well: m 36 well (ch: 3 f ages 14, 12, 1 well): f 32 well: d i sex unknown.
MF English industrial Lancashire 72 well. MM English industrial Lancashire well d 49.
M's sibs: M: m 46 well: m 39 well (ch: m 5 well): m 35 well (ch: 2 f 7 and 5, 2 m 4 and 1 well): f 32 well: m 30 well: m well d 16 Tb: m well d 5 accident.

ily 34. FF Welsh well $\overset{d}{1}$69. FFF Welsh well d old. FM English Shropshire 82 senile amnesia. FMF well d 98. FMM well d 89.
F's sibs: f d 13 months unknown: m well killed in war 32: f d 13 months unknown: m well killed in war 26 (ch: f, m adult well): m well killed in war 26 (ch: m d 2 days, m adult well): f 46 well (ch: m d 13 days, f 15, m 7, f 3 well): F:
MFScot Fraserburgh well 74. MM Scot Edinburgh well d 68.
MMF Scot Edinburgh well d 52. MMM well d 75.
M's sibs: M: m 39 well: m 36 well (ch: m 6 well).

ily 35. FF English Lancashire well d 56. FM English Lancashire well d 60 to 70.
F's sibs: f well d 50: m 67 well: F: f 64 well (ch: 2 m, 2 f well): m 63 well: f 62 well: m 53 well (ch: f 15 well).
MF French Swiss well d 56. MM French Swiss well d 50 seizure.
M's sibs: m 68 well (ch: f d 18 meningitis, f adult well): m well d 61 (ch: f adult well): m 65 well (ch: m, 3 f adult well): f well d43: (ch: 3 m adult well, m well d 30, f well adult): M: m well d 50: m 58 well (ch: 2 m, 2 f well youngest 22): m well d 53 (ch: 4 m, f adult well): f 54 well (ch: f d child infantile paralysis,m 23 well): m well d 20 to 30 pneumonia: male twins d 1 month.

ily 36. FF North Irish well d 60 to 70. FM Scot Ayrshire well d 60 to 70.
F's sibs: F mild paranoid: f 54 well (Ch: 4 m adult well):
MF Glasgow Scot well d 84. MM Scot well d 81.
M's sibs: 2 f d i unknown: f 68 well (ch: many adult well): f 66 well (ch:f 38, m 23 well): f well d 59 (ch: 7 adult well): m well (ch: 3 m, f adult well): M: m well d 44 pernicious anaemia (ch:m, f adult well).

ly 37. FF English Lancashire well d 66. FM Scot 77 well.
F's sibs: F: m 43 well (ch: f 19, f 18, m 15 well): f 40 well (ch: m 13, m 10 well). 6 female half sibs all over 50 well.
MF Irish well d adult. MM Irish well d 64.
M's half sib: f 46 well.

ily 38. Half sibs: f 53 well: f 52 well: f adult well: m d i unknown.
FF English Lancashire well d 45. FM English Lancashire well d 50 to 60.
F's sibs: order unknown. f well: 5 m well: m 70 dullard.
Maternal ancestors were English. M's sibs: Several unknown:
m well d 50 to 60: f well d 50 to 60.

ily 39. FF South West Ireland well d old. FM South West Ireland well d old.
F's sibs: order unknown: 3 m adult unknown (ch: unknown); 4 f adult unknown (ch: unknown): m d i.
MF English Lancashire well d adult accident. MM English Chester well d 69.
M's sibs: order unknown: 4 f well d 50 to 60 (ch: unknown): m well killed in war adult: m adult well (ch: unknown)

ily 40. FF Irish well d 42. FM well d 52.
F's sibs: order unknown: m 63 well (ch: 2 m, f, twin m adult well): f well d 62 (ch: 3 m, f adult well): f 49 well (ch: m well): f 48 well: f adult unknown.
MF unknown. MM English well d 76.
Male half sib of mother adult well.

ily 41. FF English Lancashire well d 83. FM English Lancashire well d 78.
F's sibs: f well d 50 (ch: 2 m adult well, f well d adult): m well d 50 (ch: 3 m, f adult well): m well killed in war 41: f 57 well: F: f 54 well (ch: m well killed in war 25, m 14, m 12 well): m 52 well (ch: 2 f in teens well): m 50 well (ch: m 21, f 19 well): f d i unknown: f 46 well (ch: m,f well).
MF English Lancashire well d 82. MM English ~~Lancashire~~ Londoner 84 well.
M's sibs: f 63 well (ch: m killed in war, 3 f, 2 m adult well): f 61 well (ch: m 42 well): f 59 well (ch: 6 m, 6 f well): f 56 well (ch: m, 2 f well): M: m d i unknown: m 52 well: m 50 well (ch: 4m, 2 f well): f 47 well (ch: f 14, m 1 well): f 45 well (ch: 2 f, 3 m well)

ily 42. Half sib f 9 well.
FF Irish County Cork 70 well. FM English Lancashire well d 50.
F's sibs: f 48 well (ch: 4 well sex unknown): f 46 well (ch: f adult well): m 44 well (ch: 2 m, 5 f well eldest 22): m 42 well (ch: m adult well): F: f 34 well (ch: 2 m, 2 f well).
MF English Somerset well d 63. MM English Derbyshire well d 56.
M's sibs: m 69 well (ch: m well): m 67 well: f 65 well (ch: 3 m, f well): m d 40 to 50 unknown mental disorder (ch: m well killed 23 accident): f 62 well (ch: 2 m well): f 60 well (ch: m, f well): m 58 well (ch:2 f, m well): f 54 well (ch: f d 17 idiot, f d 7 defective.): f 52 well (ch: 2 f well : M.

mily 43. FF English Lancashire well d young adult. FM English Yorkshire well d 84.
F's sibs: f d i unknown: F: f well d 60 (ch: m adult well).
F's half sib: f 50 well.
MF English Lancashire psychopath d 63. MFM d old insane, her brother insane in middle life. MM English well d 48.
M's sibs: f well d 79 (ch: m d i unknown, 5 m, 4 f adult well): f 76 well (ch: m d i unknown, m well killed in war, 5 m, 4 f adult well): f well d 24 Tb: f 72 imbecile: f 70 well: m 67 well: M: f well d 9 unknown: f d 16 months fits.

mily 44 FF English Lancashire well d 70. FM English Lancashire well d 65.
F's sibs: order unknown: m well d middle life: f well: f well d 30: m well killed in war: f well.
MF Swedish well drowned adult. MM English Liverpool well d 45.
M's sibs: m well d 30 to 40 pneumonia: M: m well d 5 accident: m d 18 months unknown.

nily 45. Parents English, unknown.

nily 46. FF English Londoner well d 61. FM English well d 53.
F's sibs: m 66 well (ch: m killed in war 18, m, 3 f adult well): m 64 well (ch: m, 7 f adult well): m d i unknown: f 59 well (ch: f well d 3, 2 m in twenties well): f 57 well (ch: 3 m, 3 f well, m d i unknown): f 55 well: F.
MF English Londoner well d 52. MM English Londoner well d 72.
M's sibs: f well d 30 to 40: f 57 well (ch: m 26, f 24, m 22 well): f 54 well (ch: 2 m in twenties well): M: m 49 well: m 47 well (ch: 2 f, m adult well): m well killed in war 22.

APPENDIX IV . FAMILY CHARTS .

male

female

sex unknown

several, both sexes

died under 5 years

indicates propositus

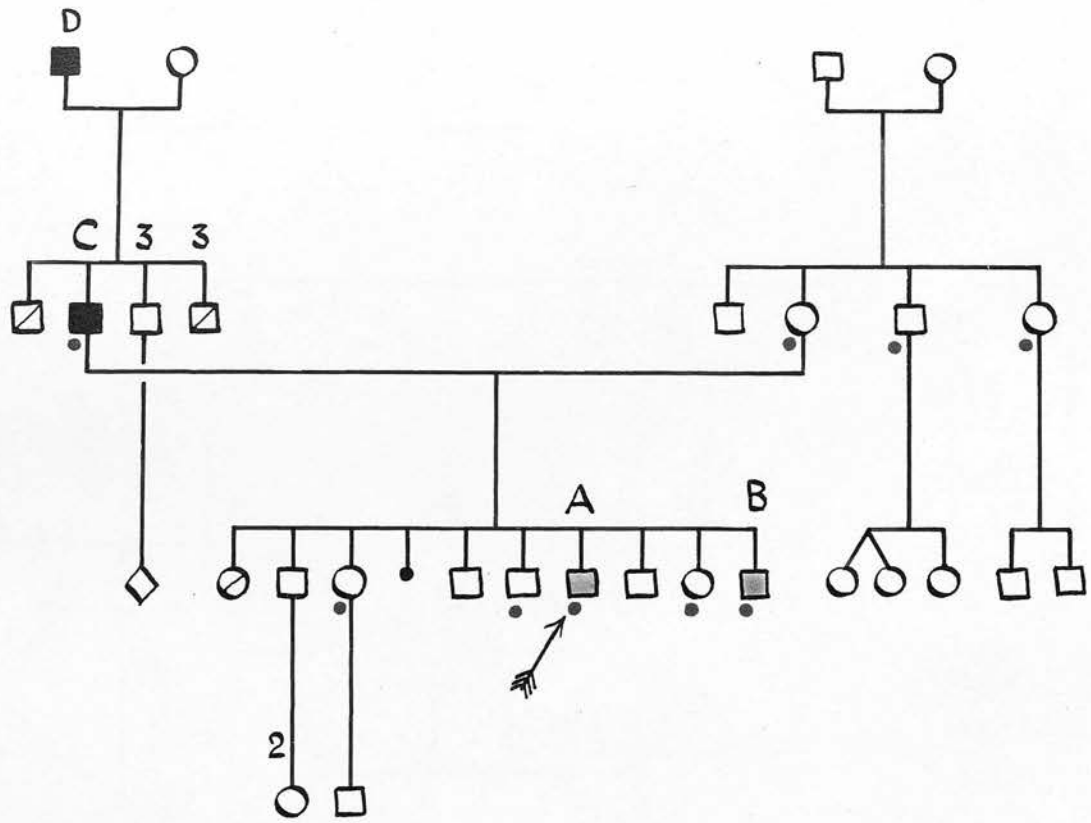
phenylketonuria

probable phenylketonuria

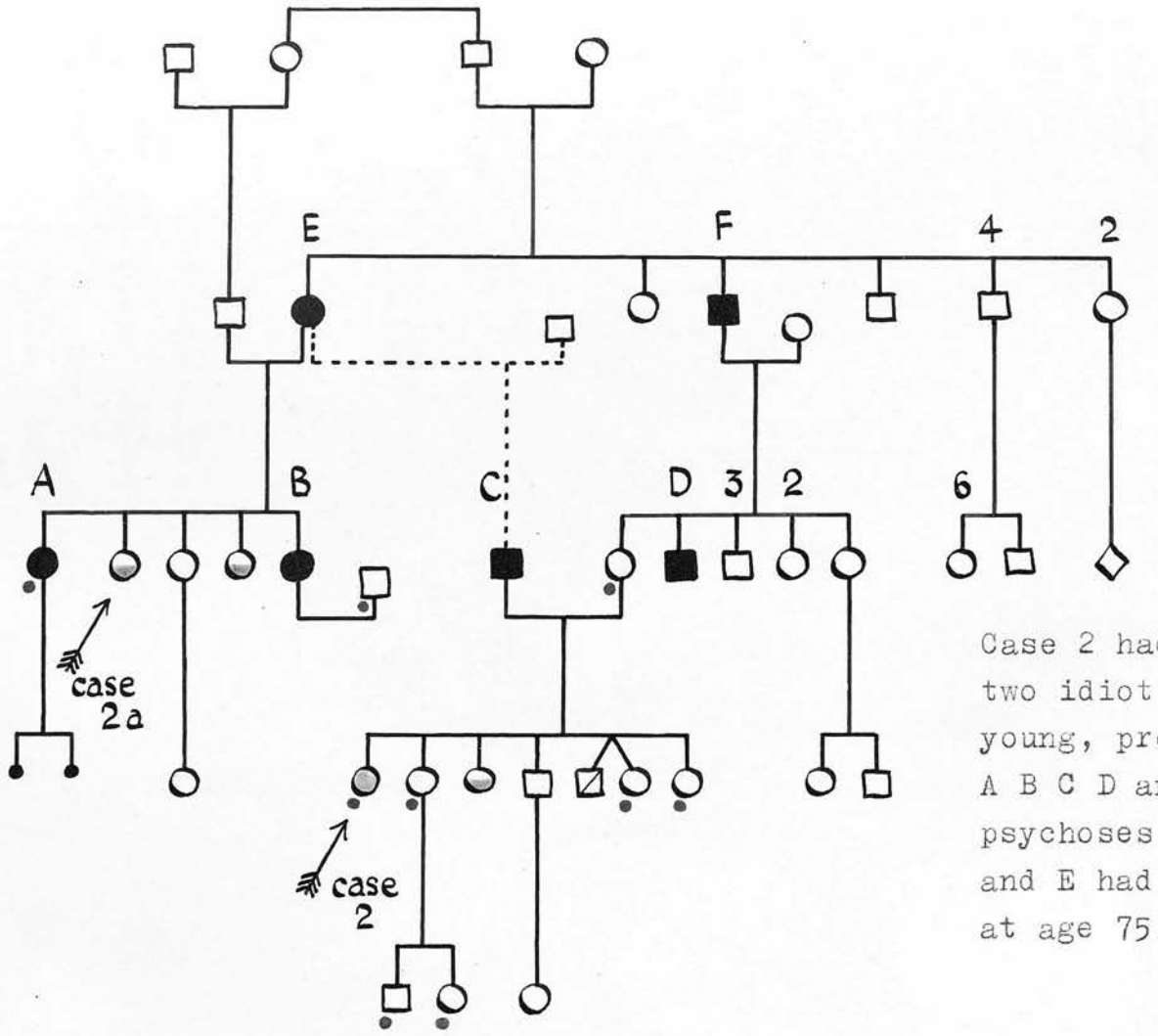
psychosis, mental defect, psychoneurosis, psychopathy and bodily disease specified on chart .

• personally examined by the author

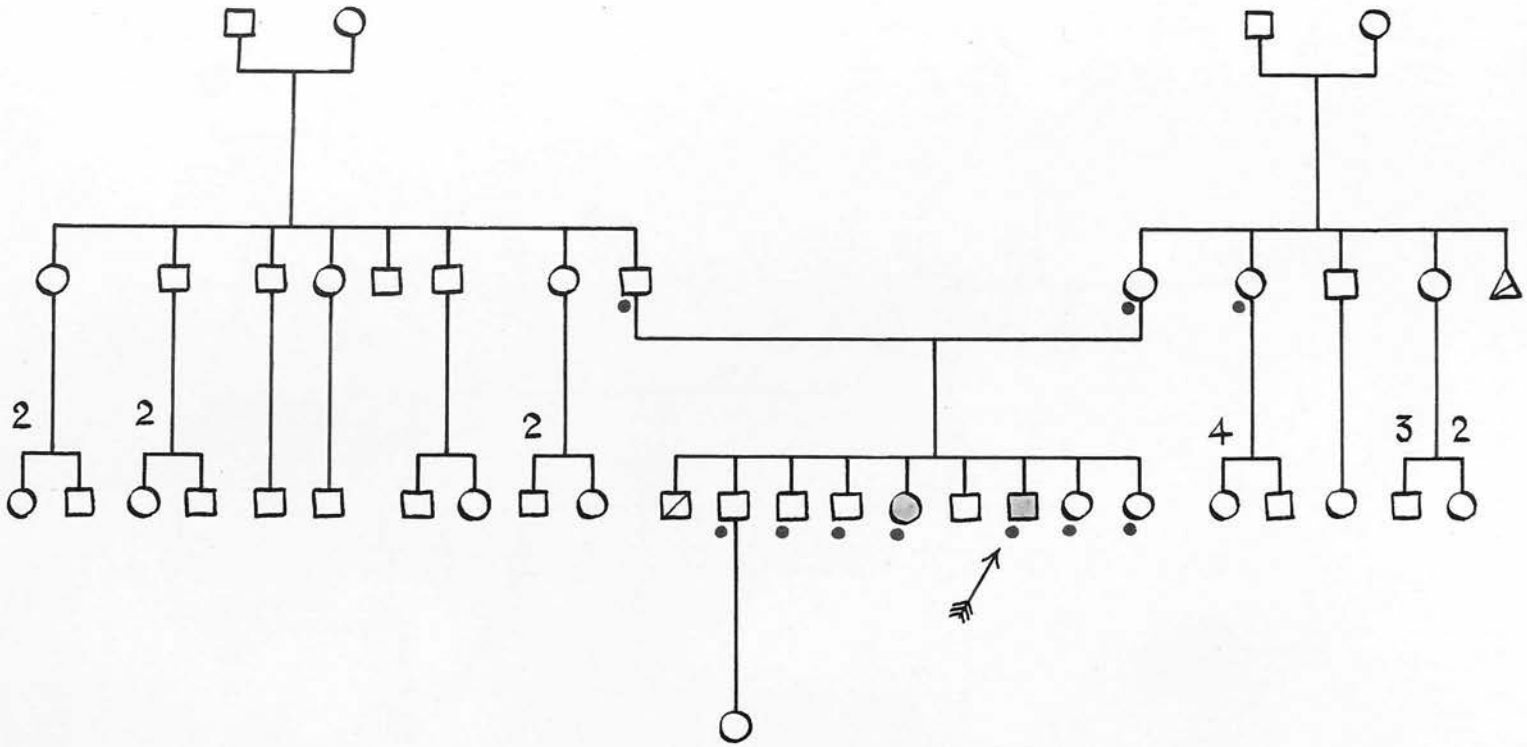
• miscarriage



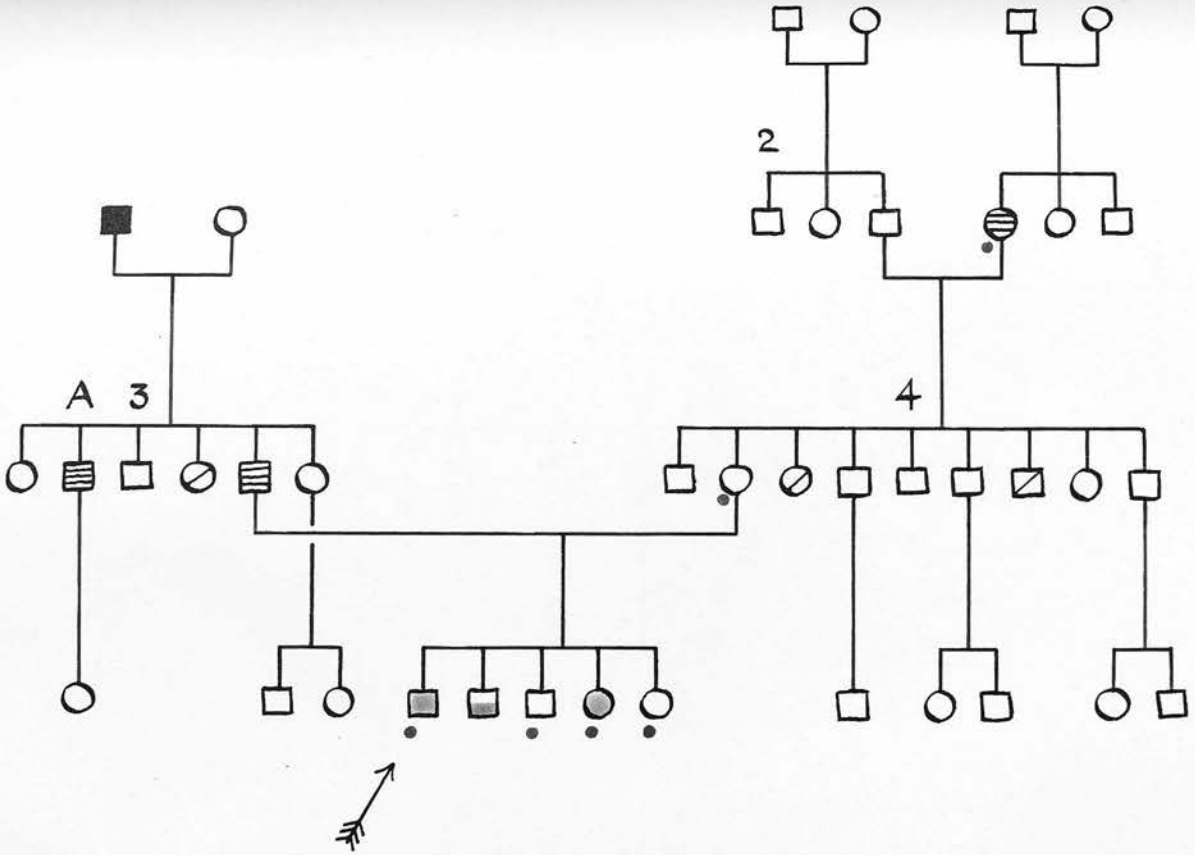
The propositus, A, has a brother, B, who is also a phenylketonuric idiot. Their father, C, and grandfather, D, had paranoid psychoses.



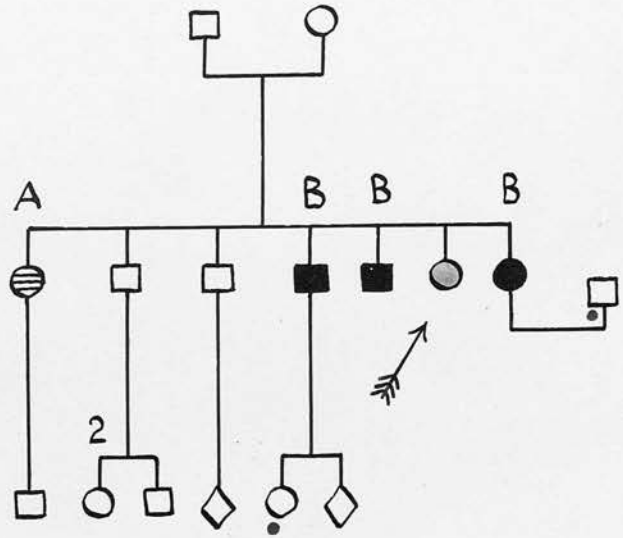
Case 2 had an idiot sister and two idiot half-aunts who died young, probably phenylketonuric. A B C D and F had depressive psychoses starting in middle life and E had a mild psychosis at age 75.



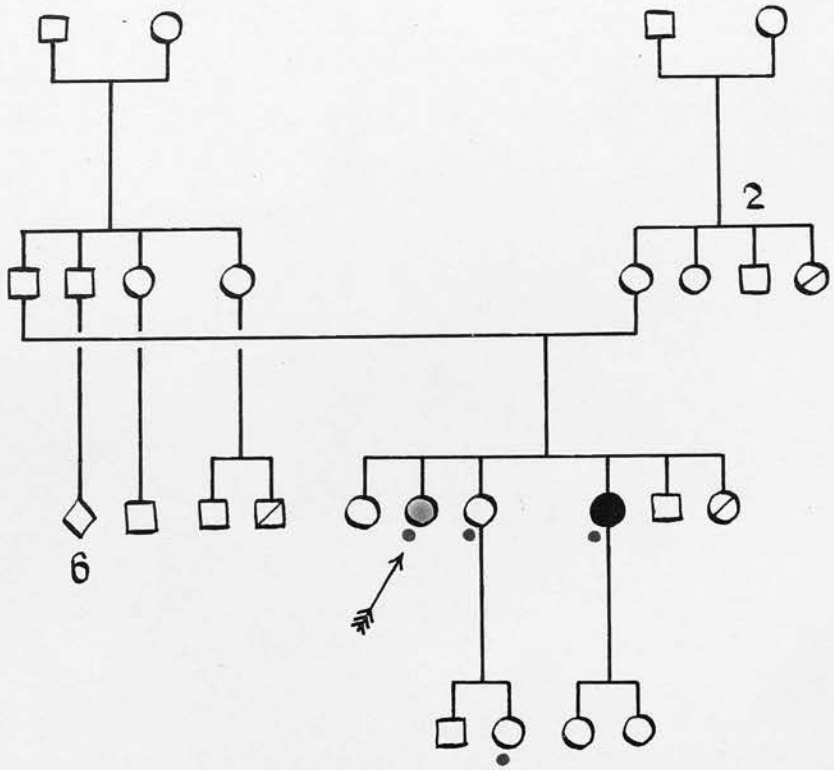
A sister of the propositus is also phenylketonuric.
The family is otherwise healthy.



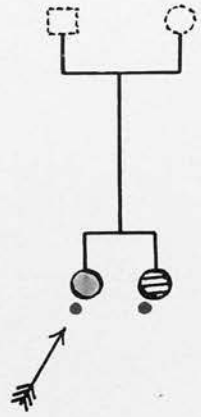
A sister was certainly and a brother probably phenylketonuric. The father was a psychopath. The paternal grandfather had a psychosis, an uncle, A, was a chronic alcoholic, and the maternal grandmother is hypomanic.



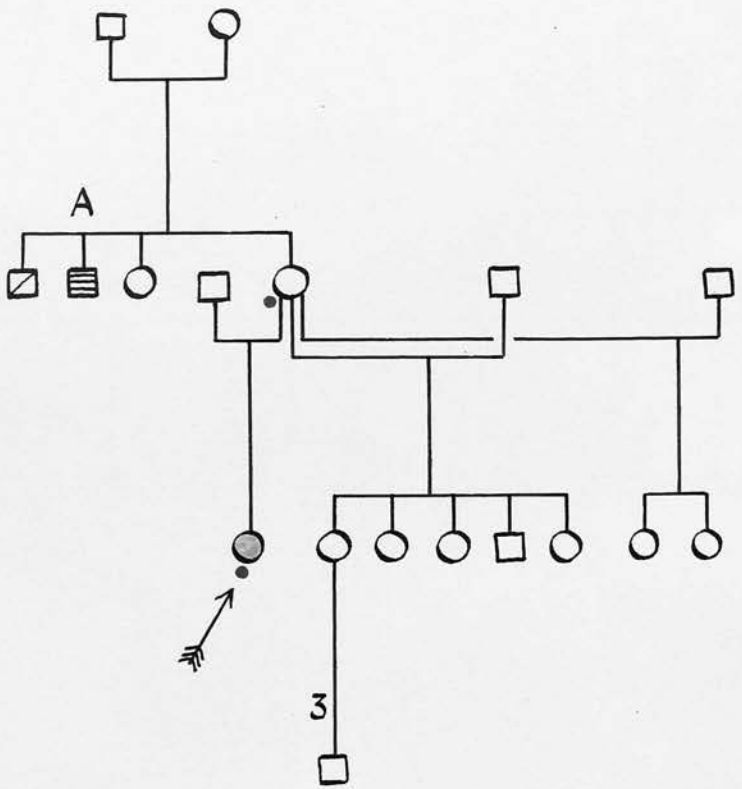
Few relatives except the sibs are known. A sister, A, had a mild depression and three sibs, B, had severe depressions.



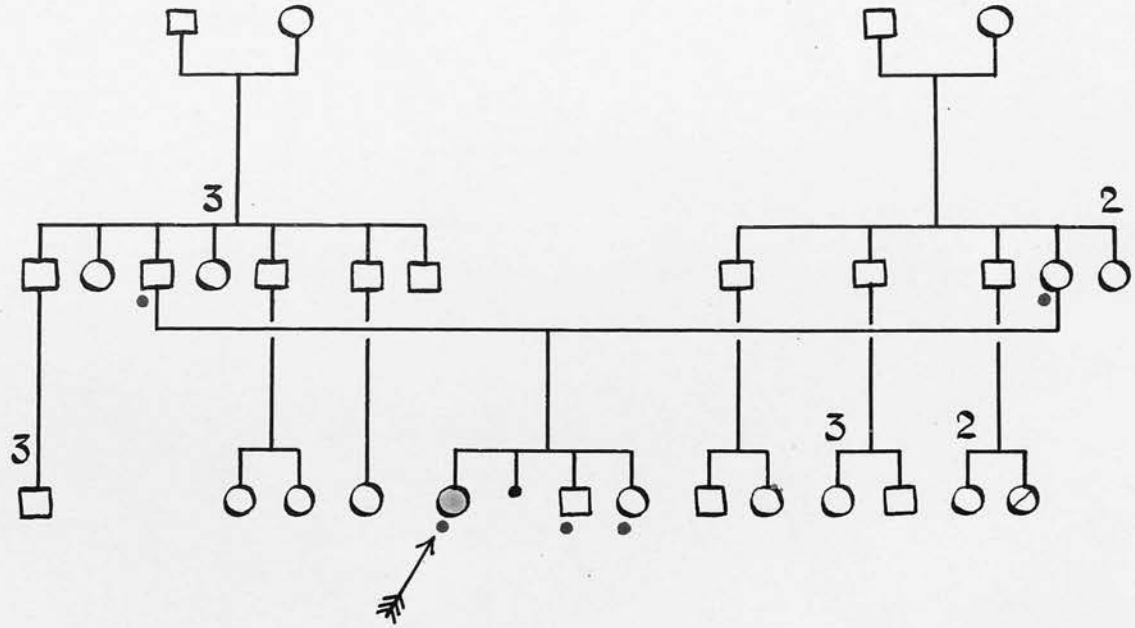
One sister had a depressive psychosis.



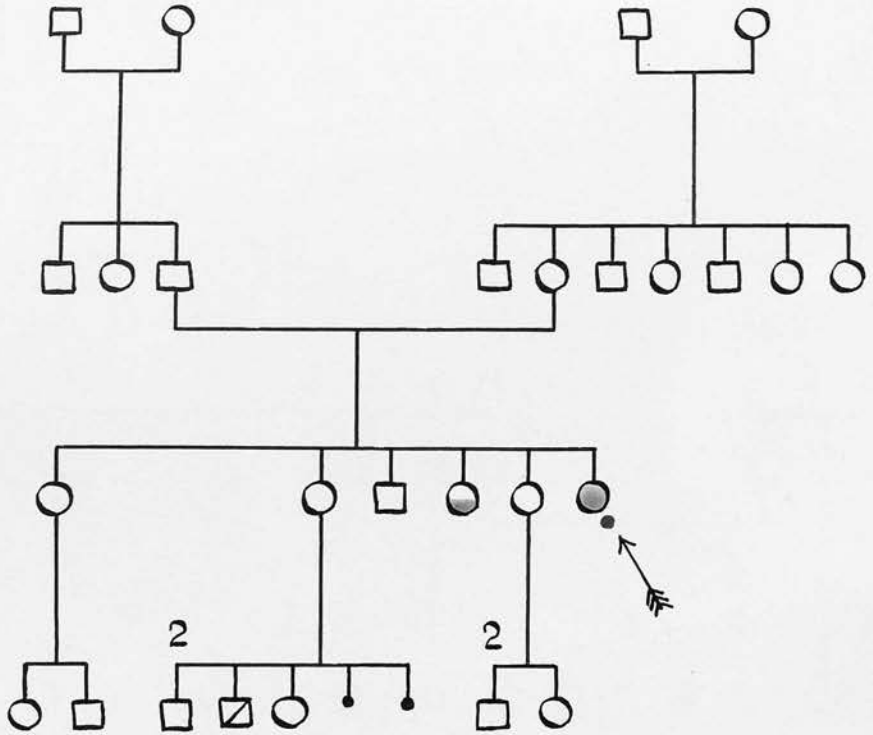
Parents unknown : sister feeble-minded
but not phenylketonuric.



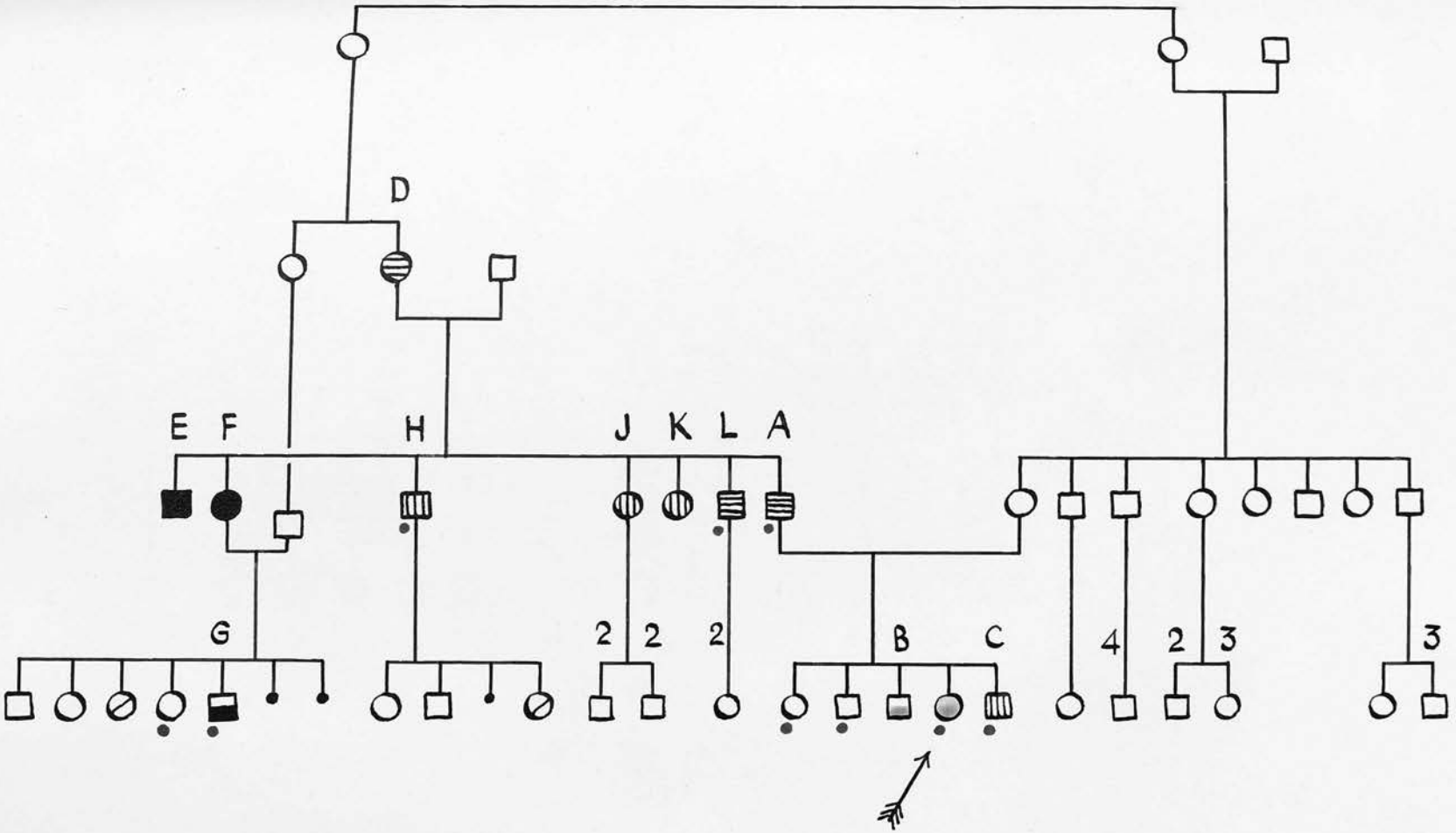
The mother married thrice. The propositus has 7 healthy half-sibs. A maternal uncle, A, was a psychopath.



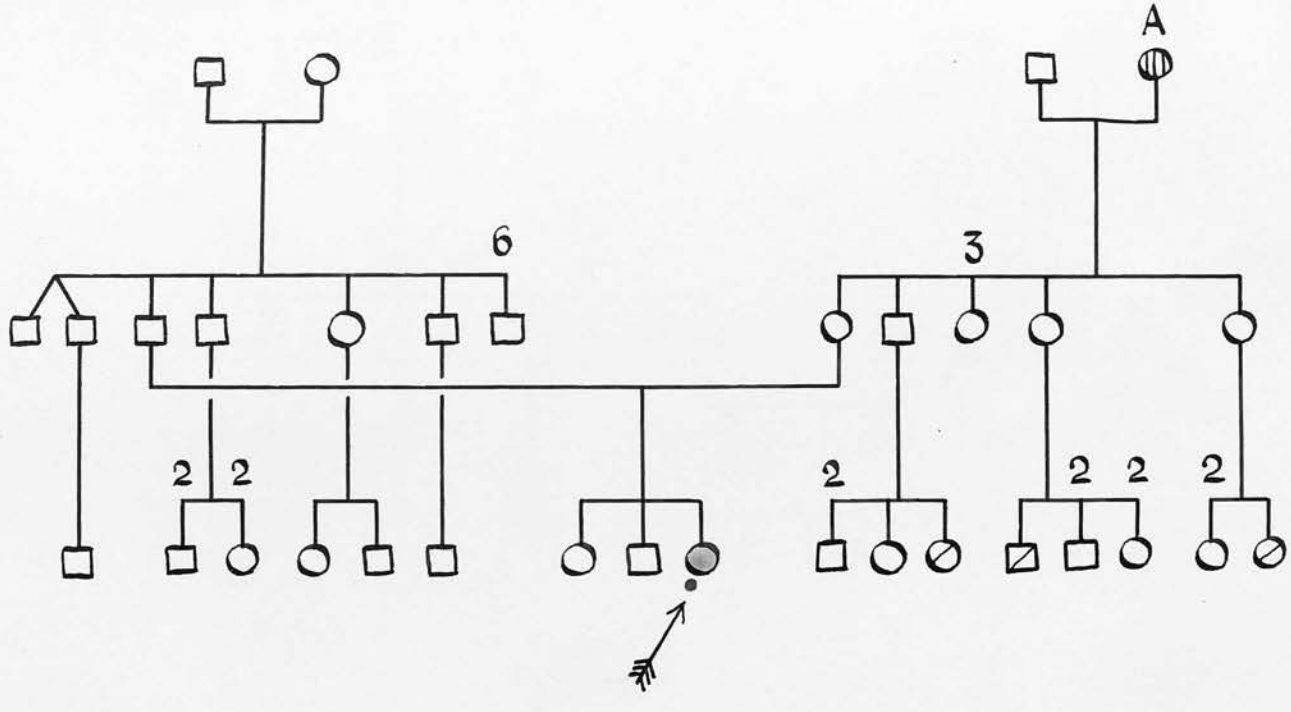
The patient has a healthy brother and sister.
One sib miscarried.



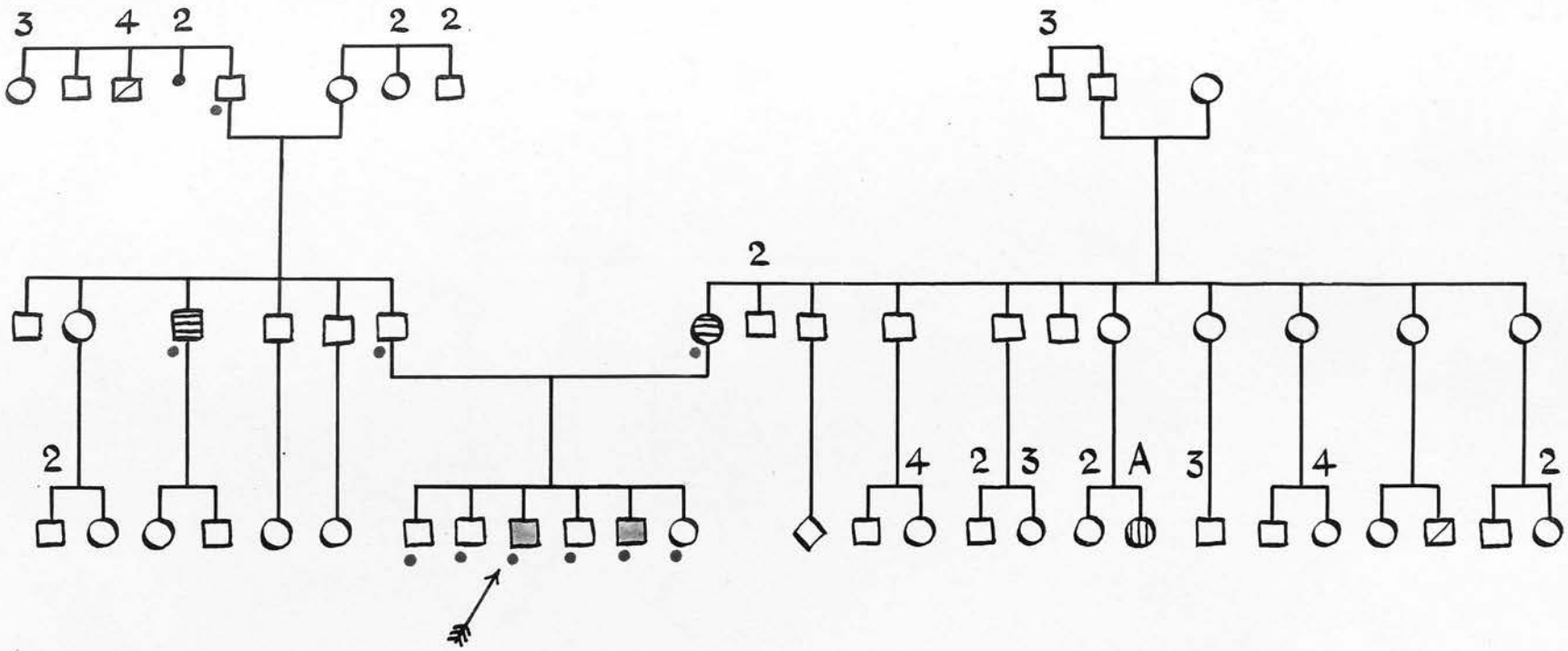
An idiot sister died aged 15, probably phenylketonuric.
The family history was obtained by letter only.



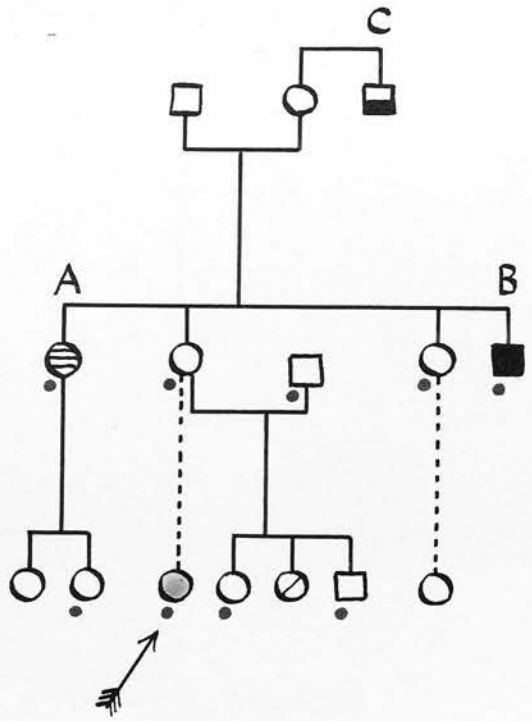
The parents are consanguineous. Thefather, A, and his mother, D, had anxiety states. A brother, B, died in infancy an idiot, probable phenylketonuric. A brother, C, had signs of diabetes insipidus. E, mild depressive psychosis. F, toxic-confusional psychosis, possible hyperthyroidism. She married her first cousin and has a feeble-minded son, G, type unknown. H, J, and K, hyperthyroidism. L, anxious hypochondriac.



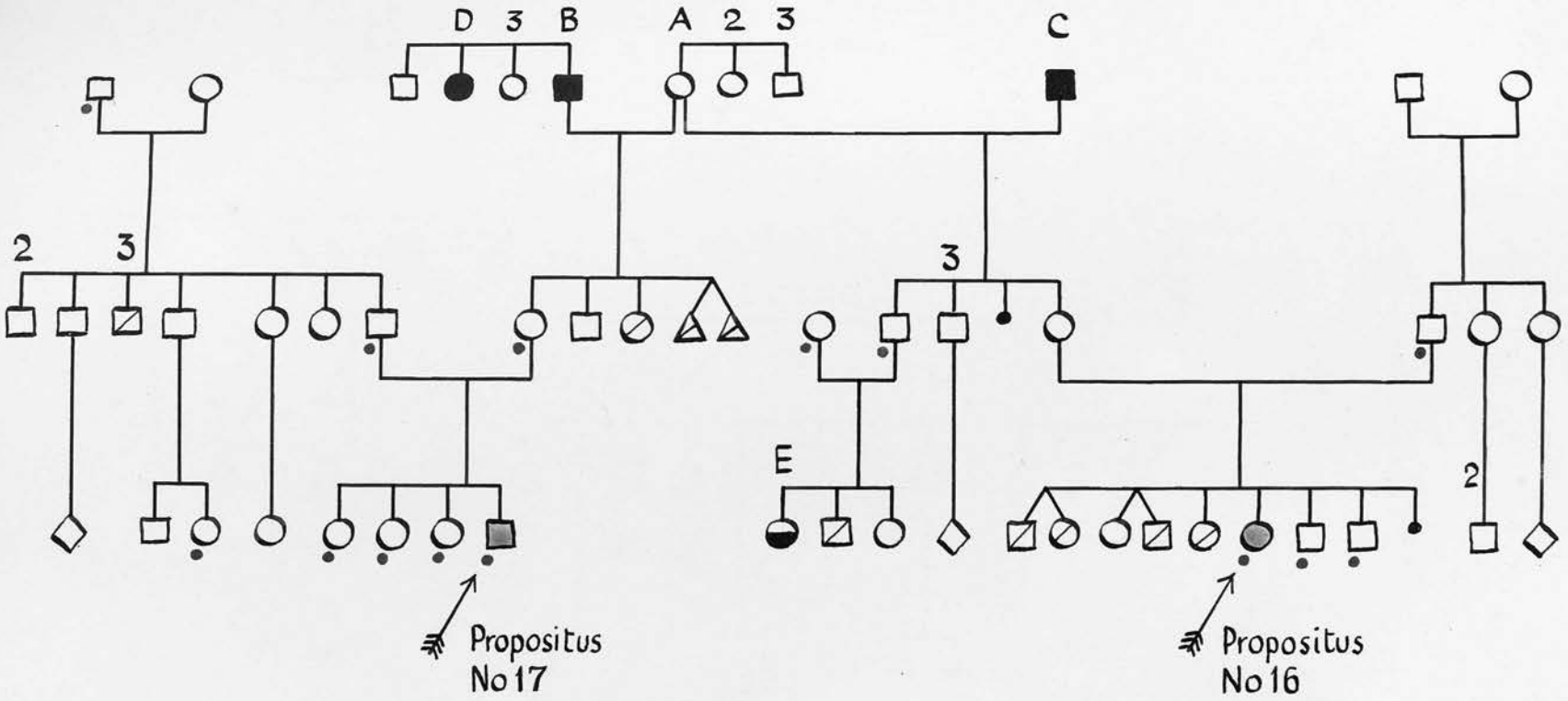
All the relatives had good mental health.
The maternal grandmother, A, had diabetes.



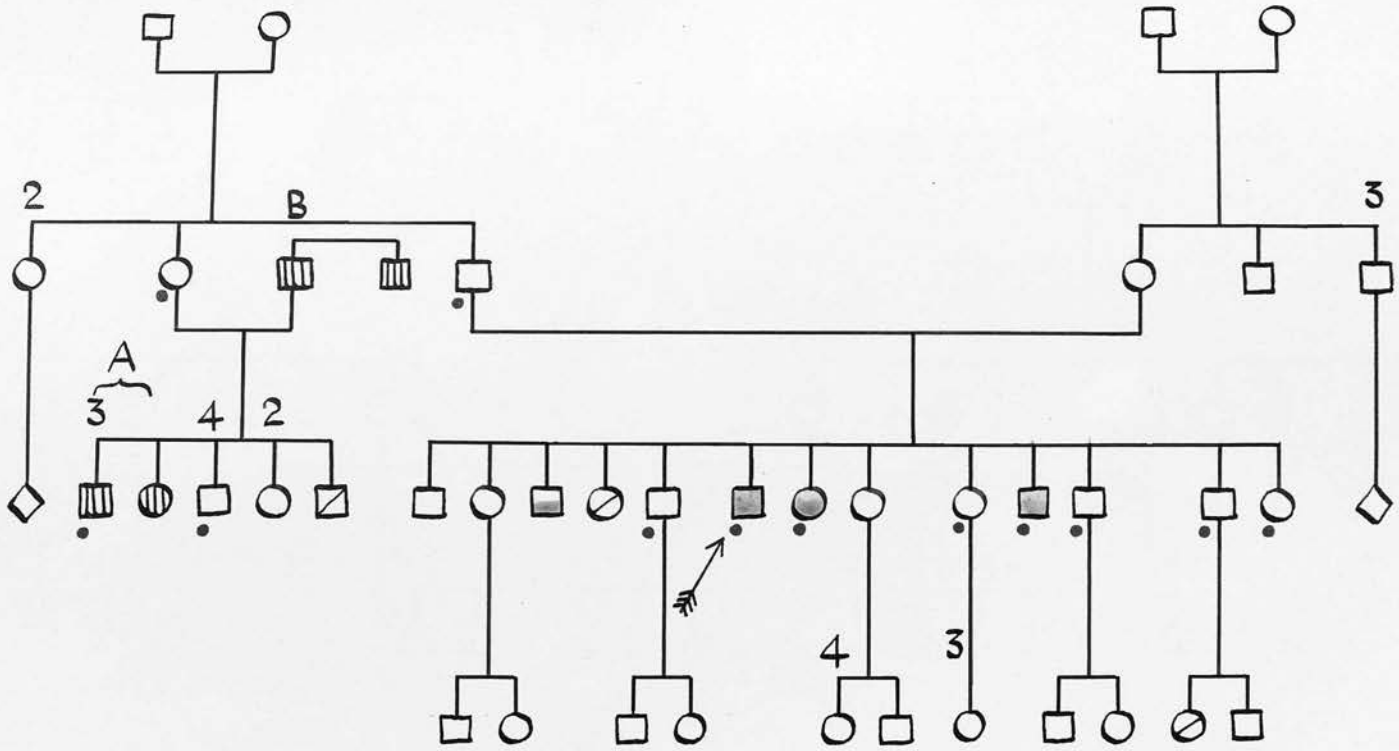
A brother is phenylketonuric and the mother has an anxiety state.
A paternal uncle has anxiety symptoms with cardiospasm.
A first cousin, A, has congenital heart disease.



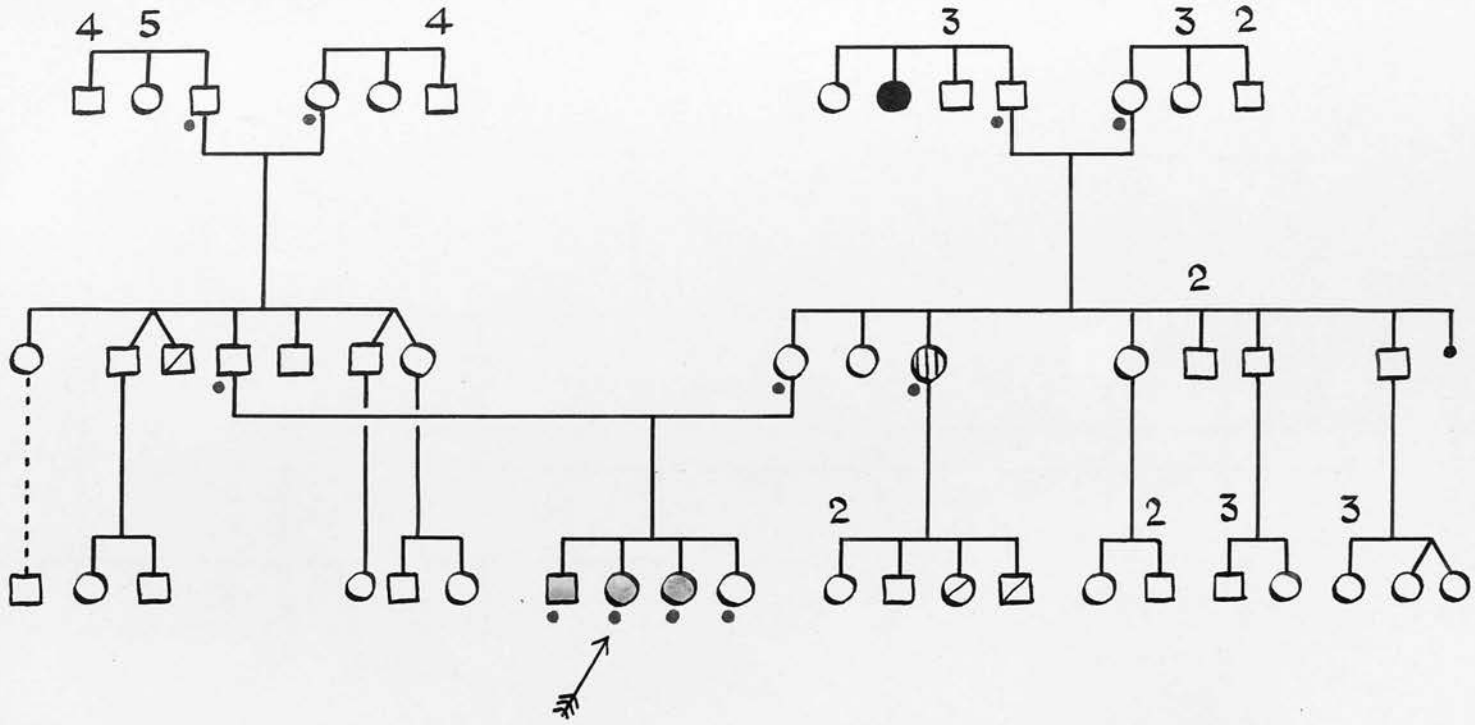
The propositus is illegitimate. An aunt, A, has an anxiety neurosis, and an uncle, B, is epileptic. A great-uncle, C, was an imbecile.



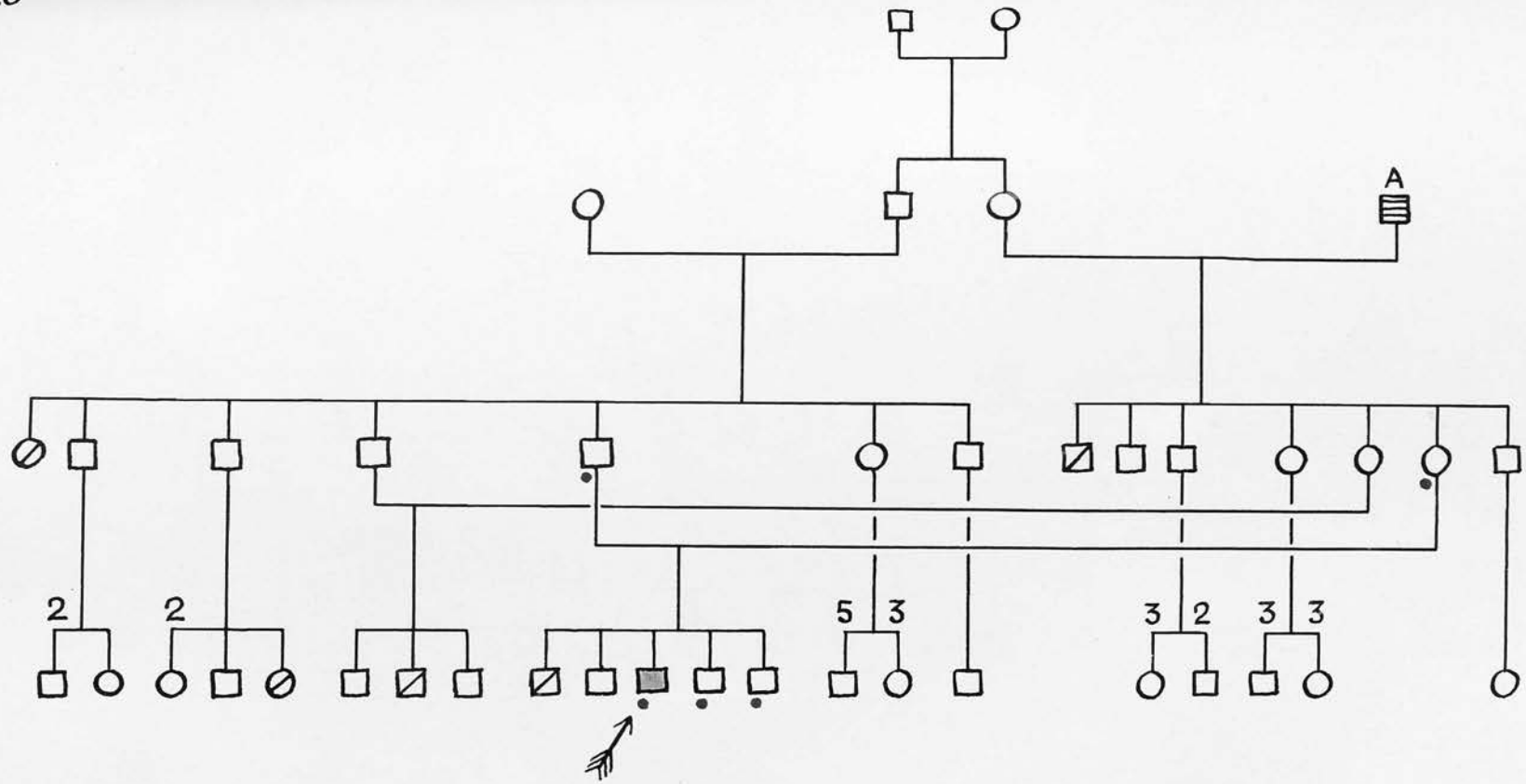
The two propositi are related through their common grandmother A.
The grandfathers, B and C, died insane in mental hospitals.
A greataunt, D, has a psychosis of organic type at age 49, and a
first cousin, E, is a feeble-minded defective, not phenylketonuric.



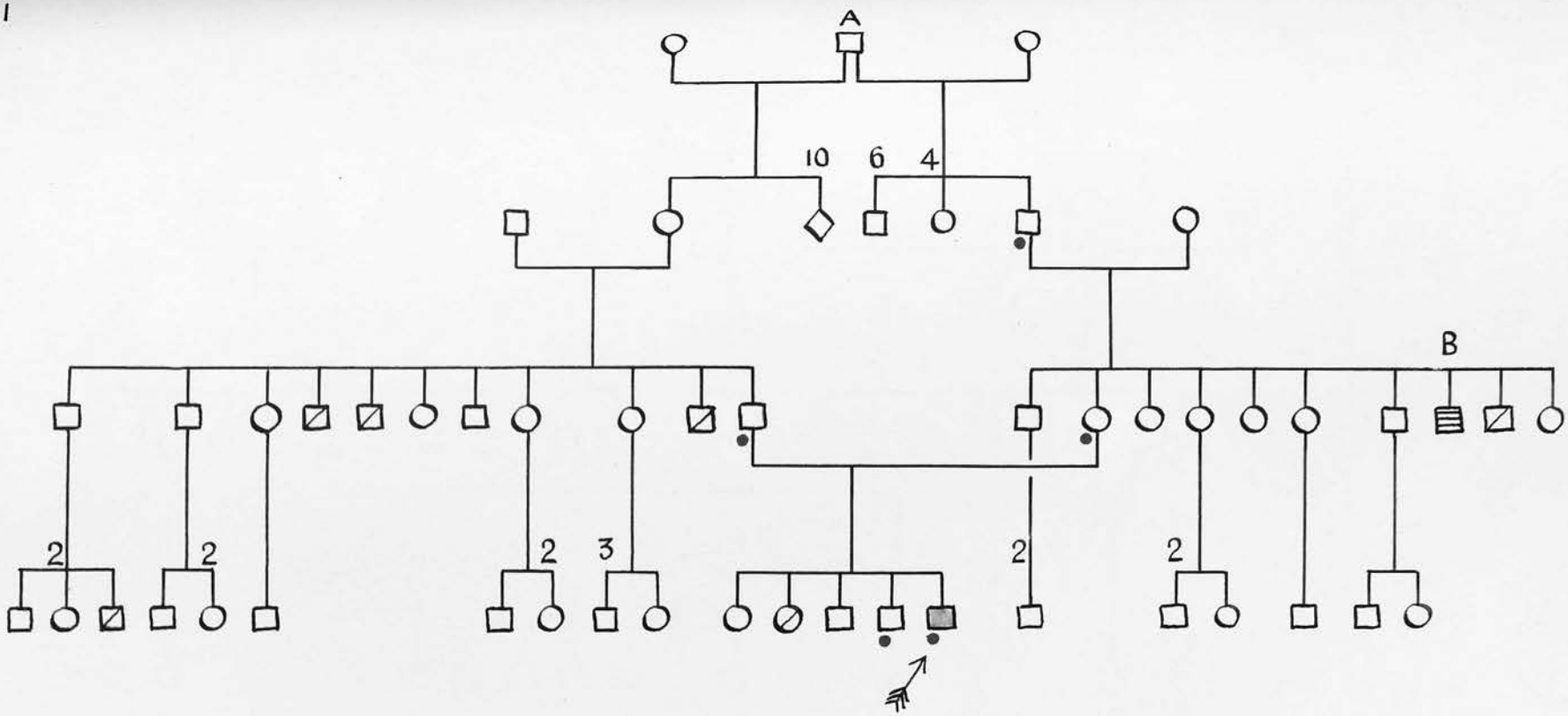
Four of a sibship of 13 were phenylketonuric. Four first cousins, A, had pseudohypertrophic muscular dystrophy which they inherited from their father, B, whose brother was also affected.



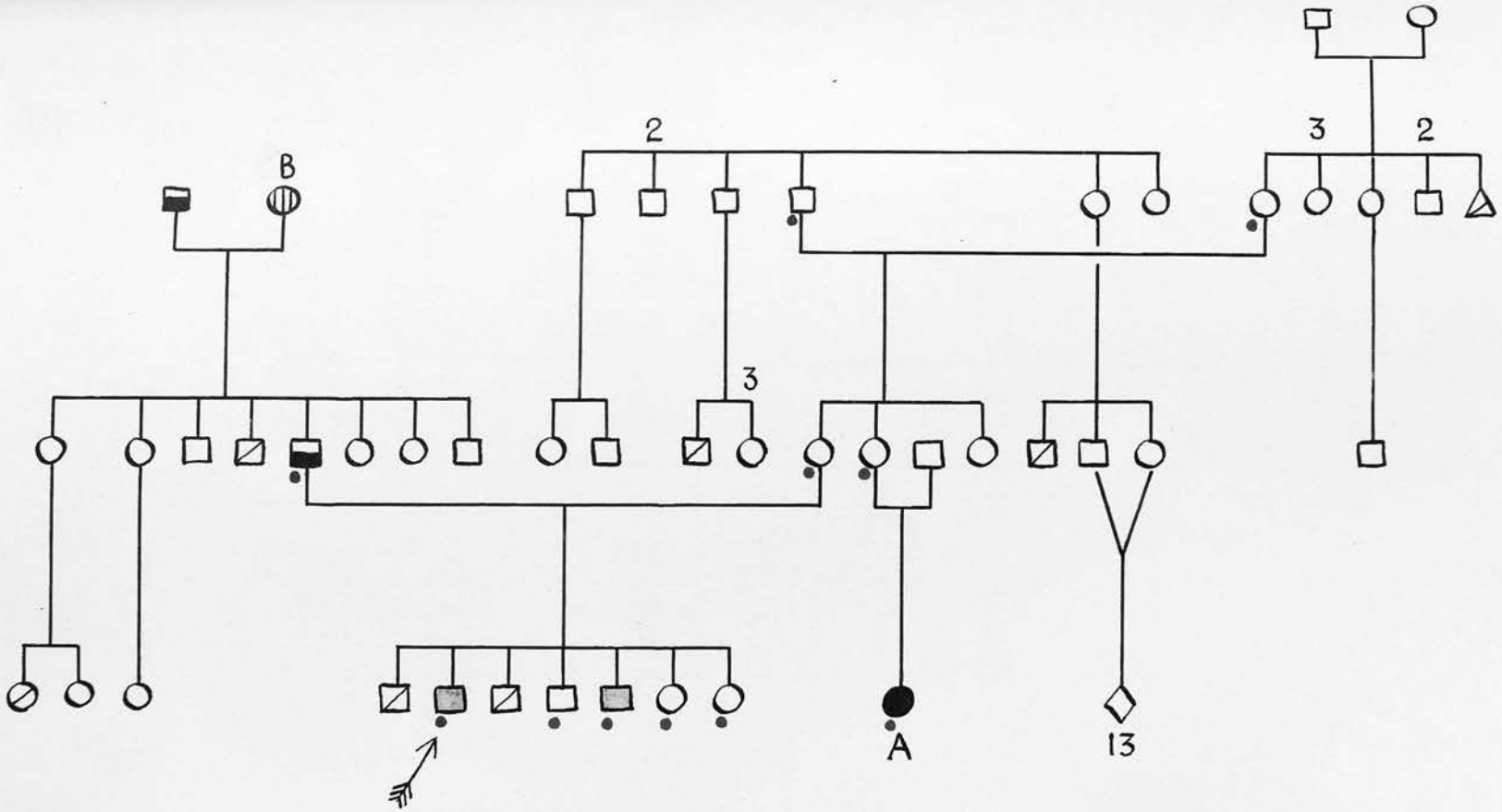
Three of 4 children have phenylketonuria.
A maternal aunt has encephalitis lethargica
with striatal rigidity, and a greataunt had
a senile arteriosclerotic psychosis.



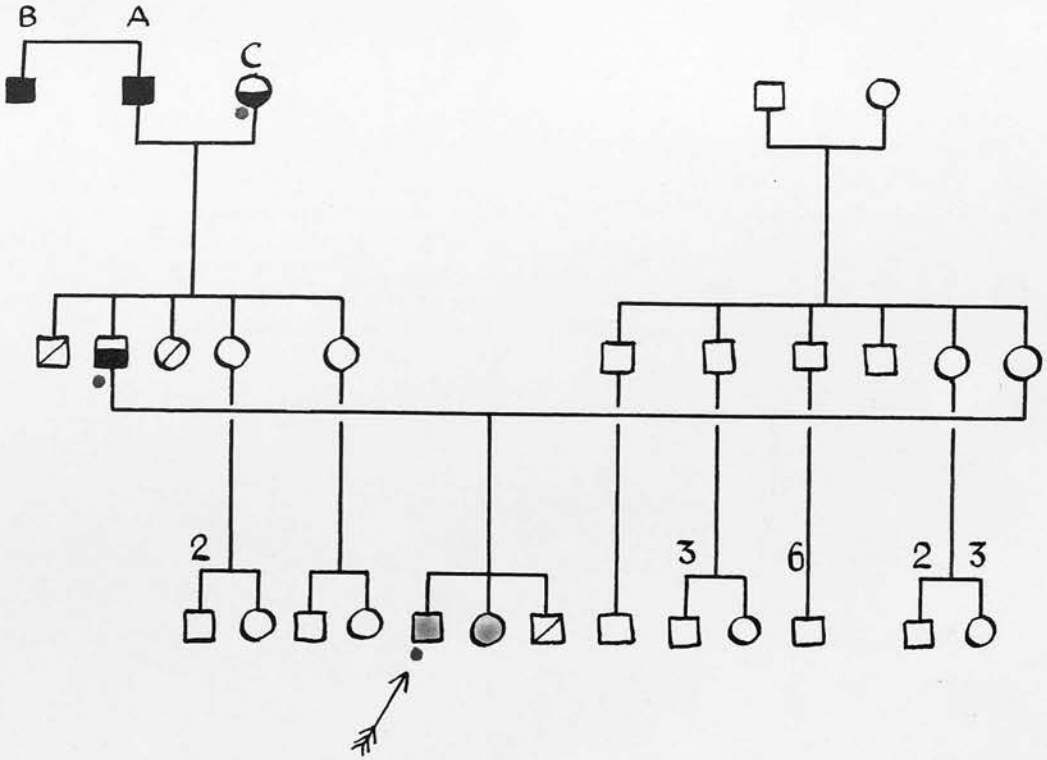
A family in which two brothers married two sisters, their first cousins. Phenylketonuria appears among the offspring of one, but not of the other couple. One grandparent, A, had possibly paralysis agitans.



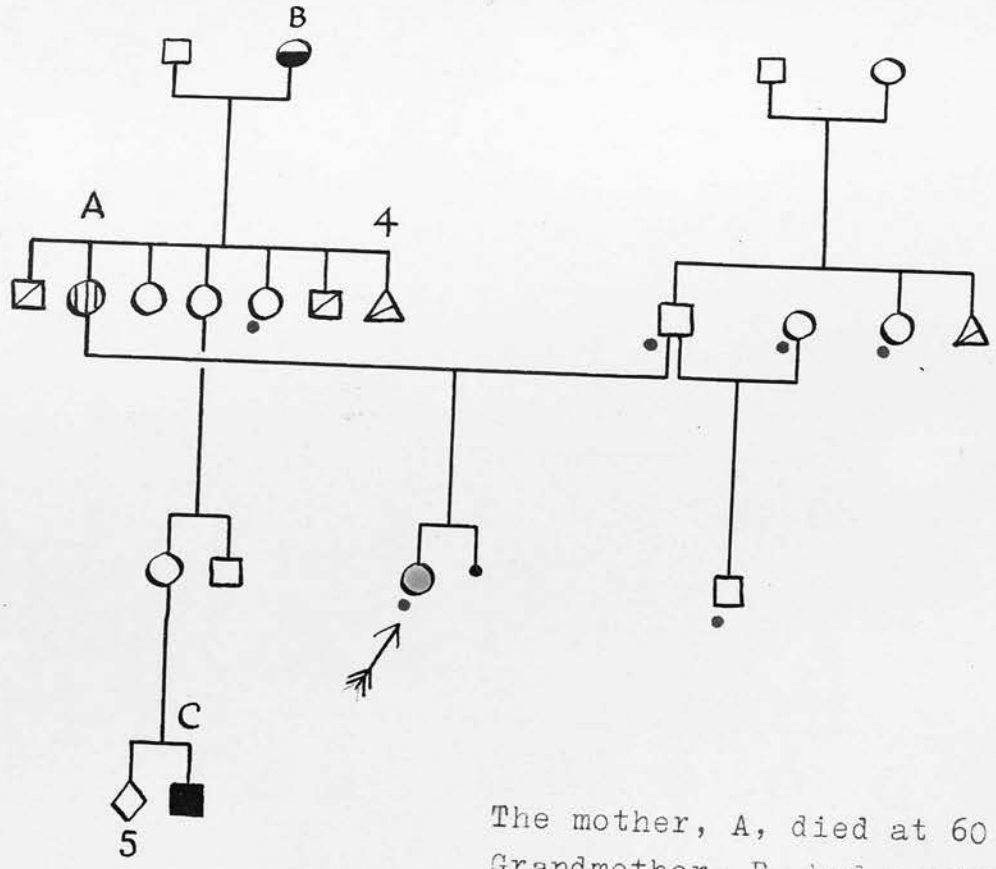
The parents are consanguineous through their common grandfather, A , who married twice. A maternal uncle, B, is feeble-minded but not phenylketonuric.



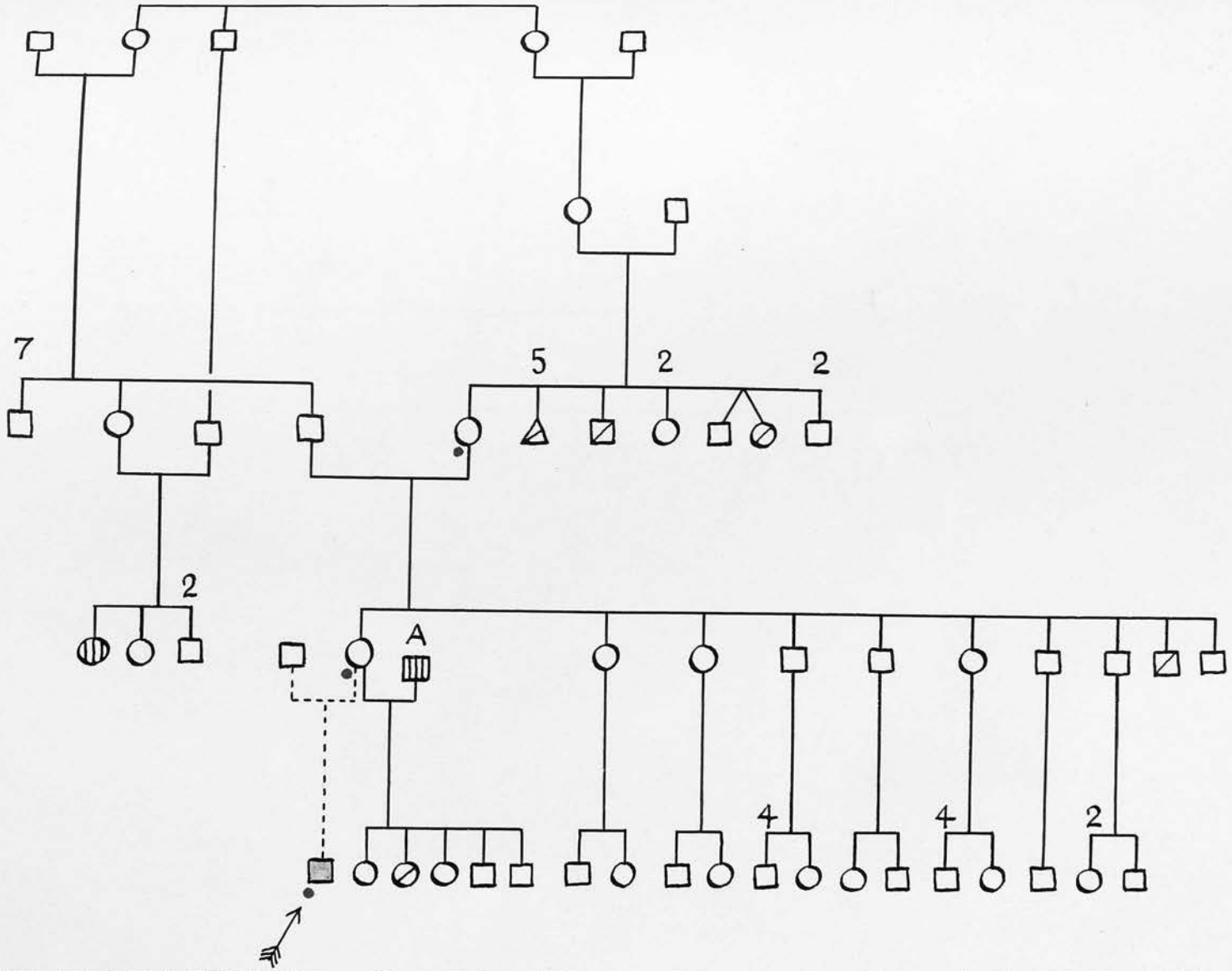
One brother has phenylketonuria. The father and grandfather are psychopathic. A grandmother, B, has diabetes. A first cousin, A, is a mongol whose parents are third cousins to each other.



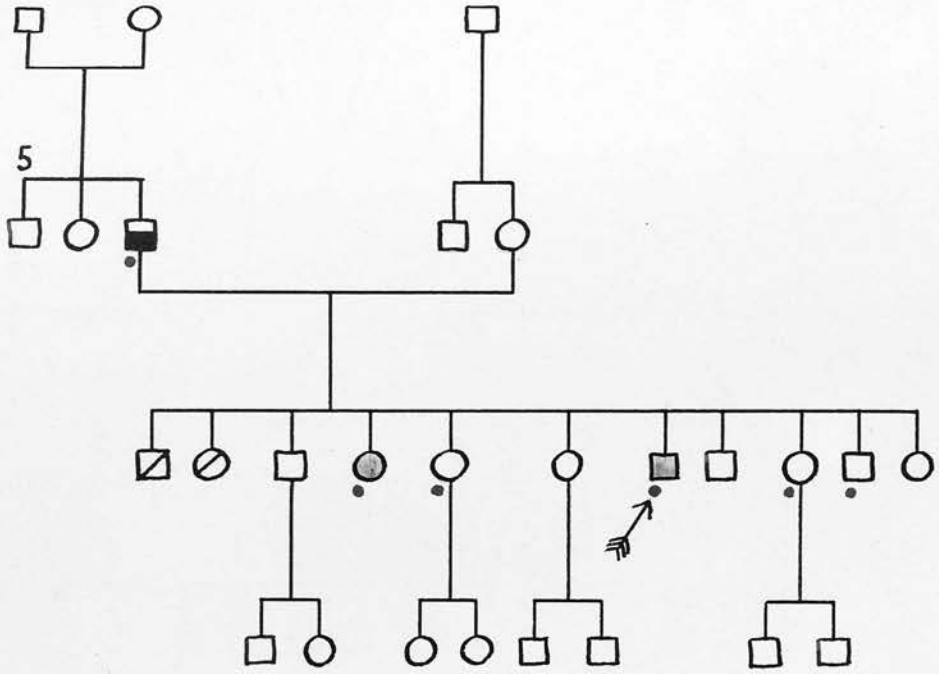
Two sibs, one a phenylketonuric idiot and the other still-born.
The grandfather, A, and his brother, B, had epileptic psychoses.
The grandmother, C, is hypomanic. The father has a mild depression.



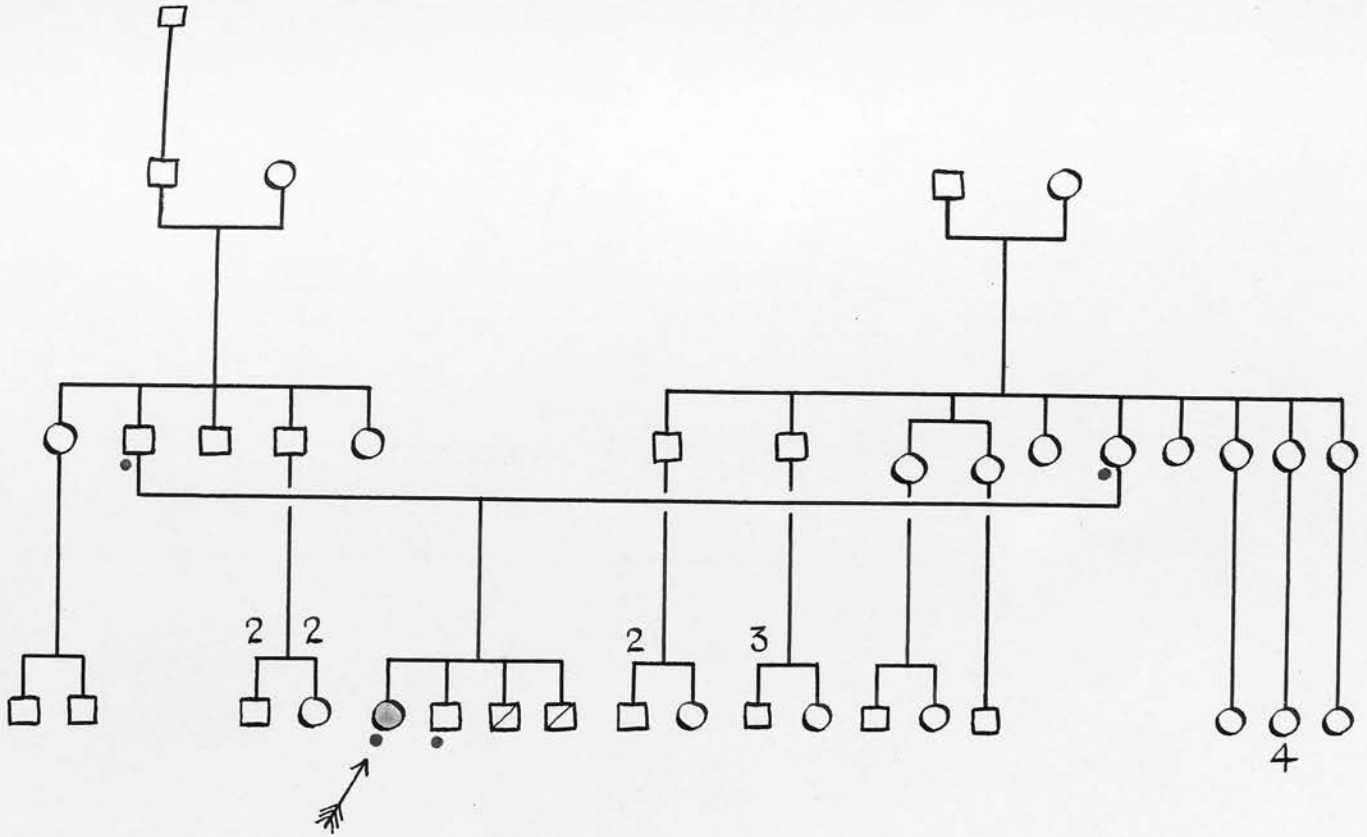
The mother, A, died at 60 of hyperthyroidism. Grandmother, B, had a mental disease and a cousin, C, is a deformed mental defective.



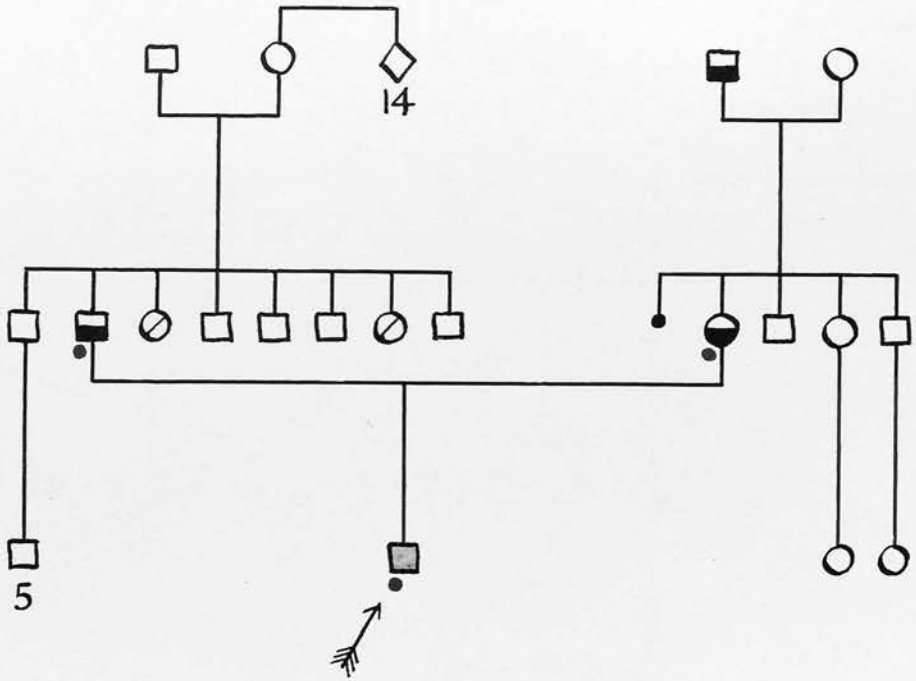
The propositus is illegitimate. The mother's parents are cousins and there is another cousin marriage in the family with one abnormal offspring, state unknown. A, died epileptic fits.



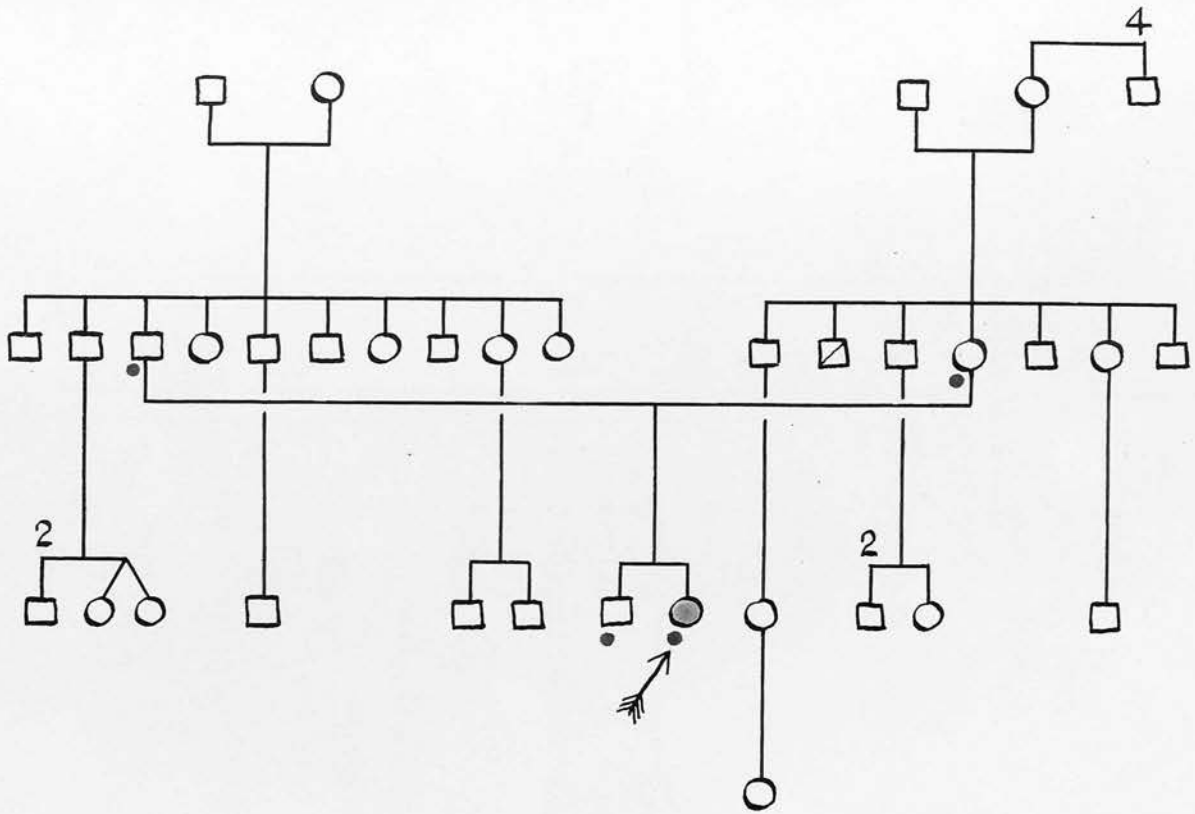
A sister has phenylketonuria. The father showed a slight mental deterioration after middle life.



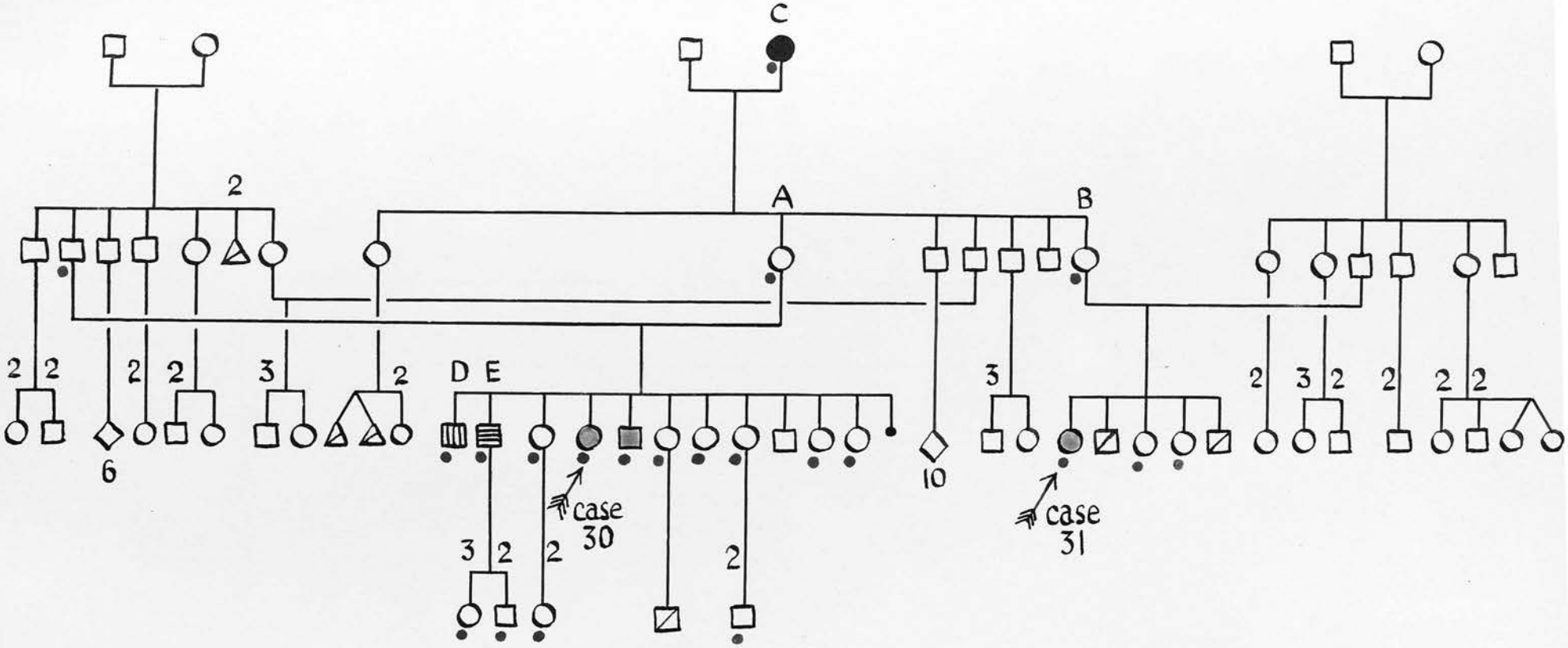
Two male sibs miscarried.



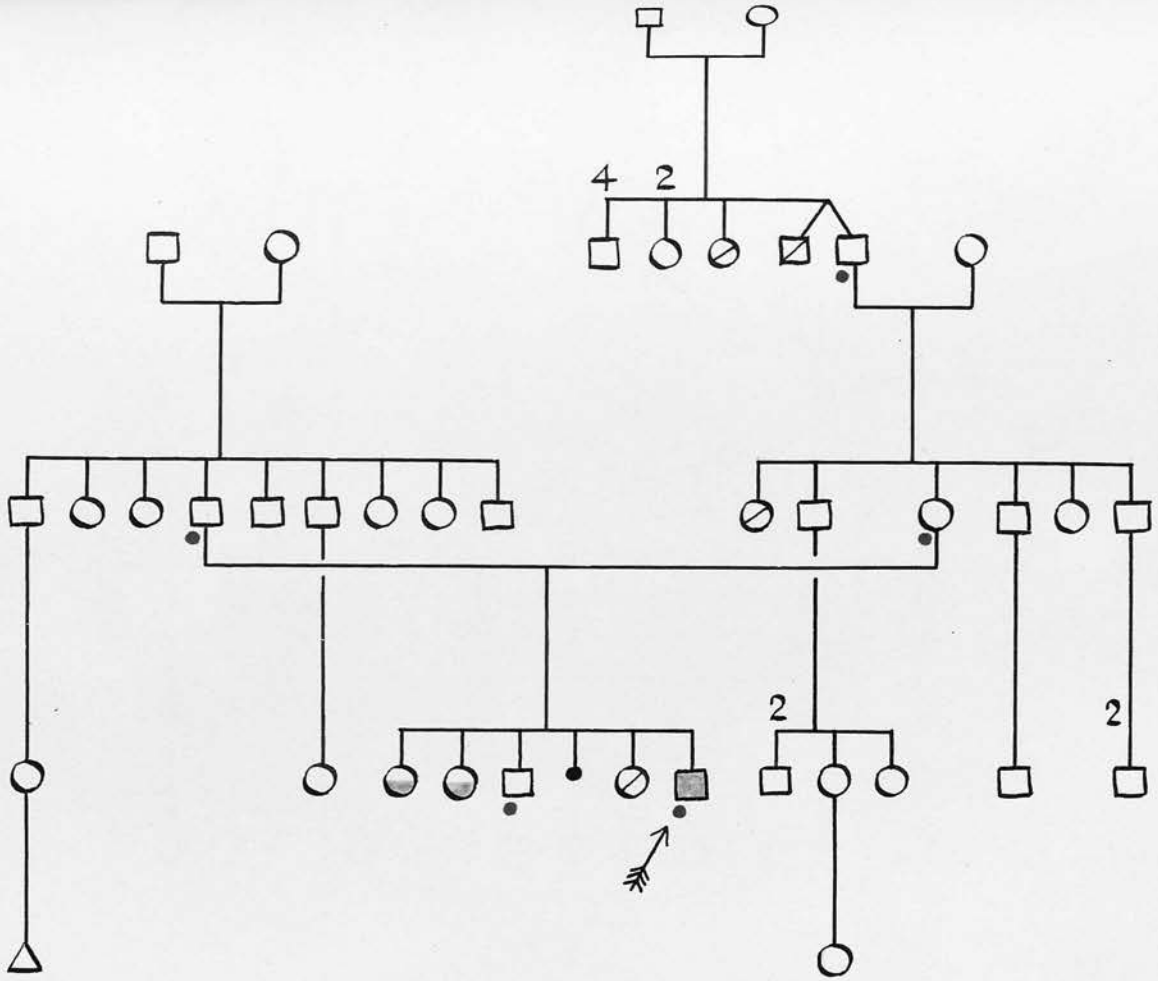
The propositus is an only child. Both parents have anxiety states and the maternal grandfather has a mild depression.



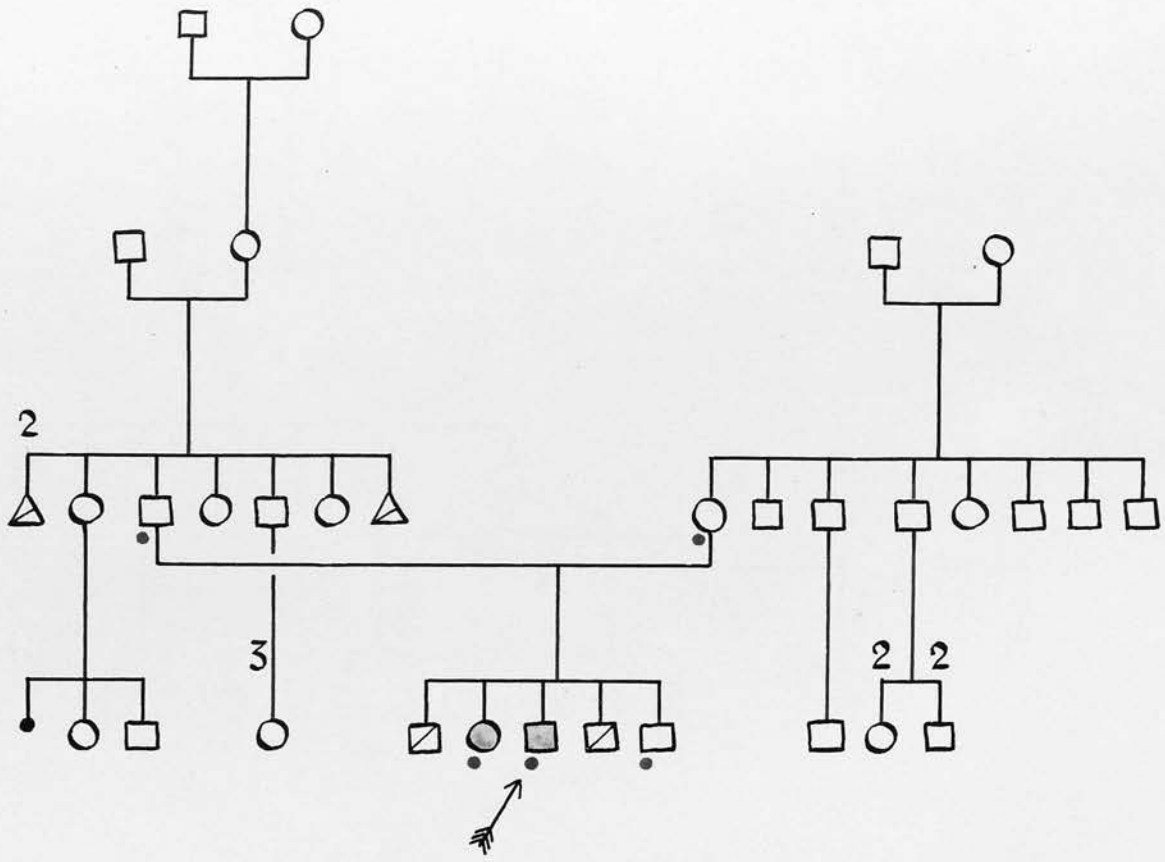
All the relatives are healthy.



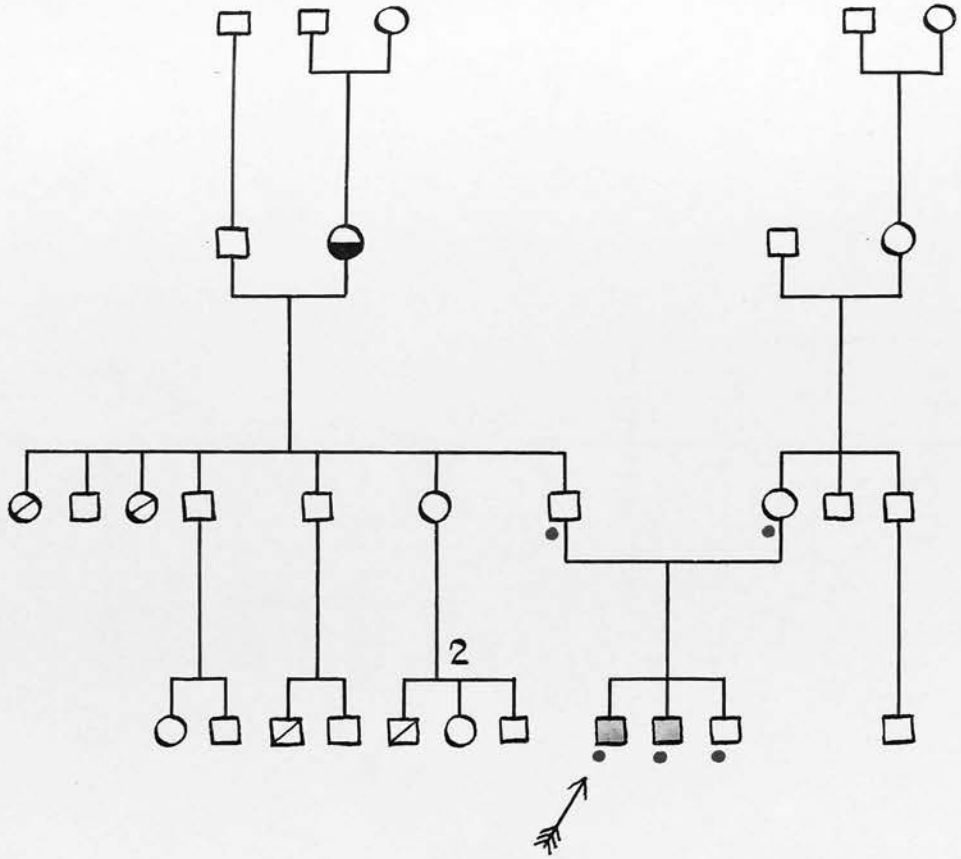
Propositi 30 and 31 are first cousins through their mothers, A and B, and their common grandmother, C, is psychotic. Patient 30 has an idiot phenylketonuric brother, a hyperthyroid brother, D, and also a feeble-minded brother who is not phenylketonuric.



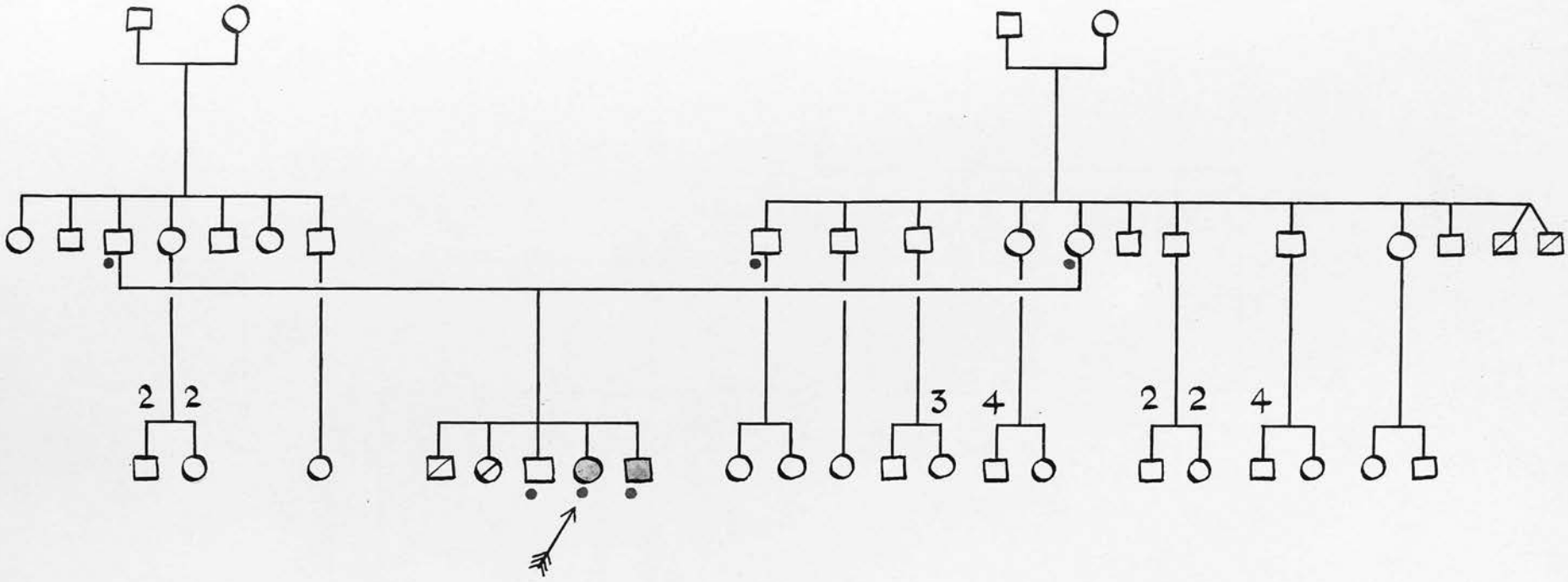
Two epileptic idiot sisters
died in mental hospital,
probably phenylketonuric.



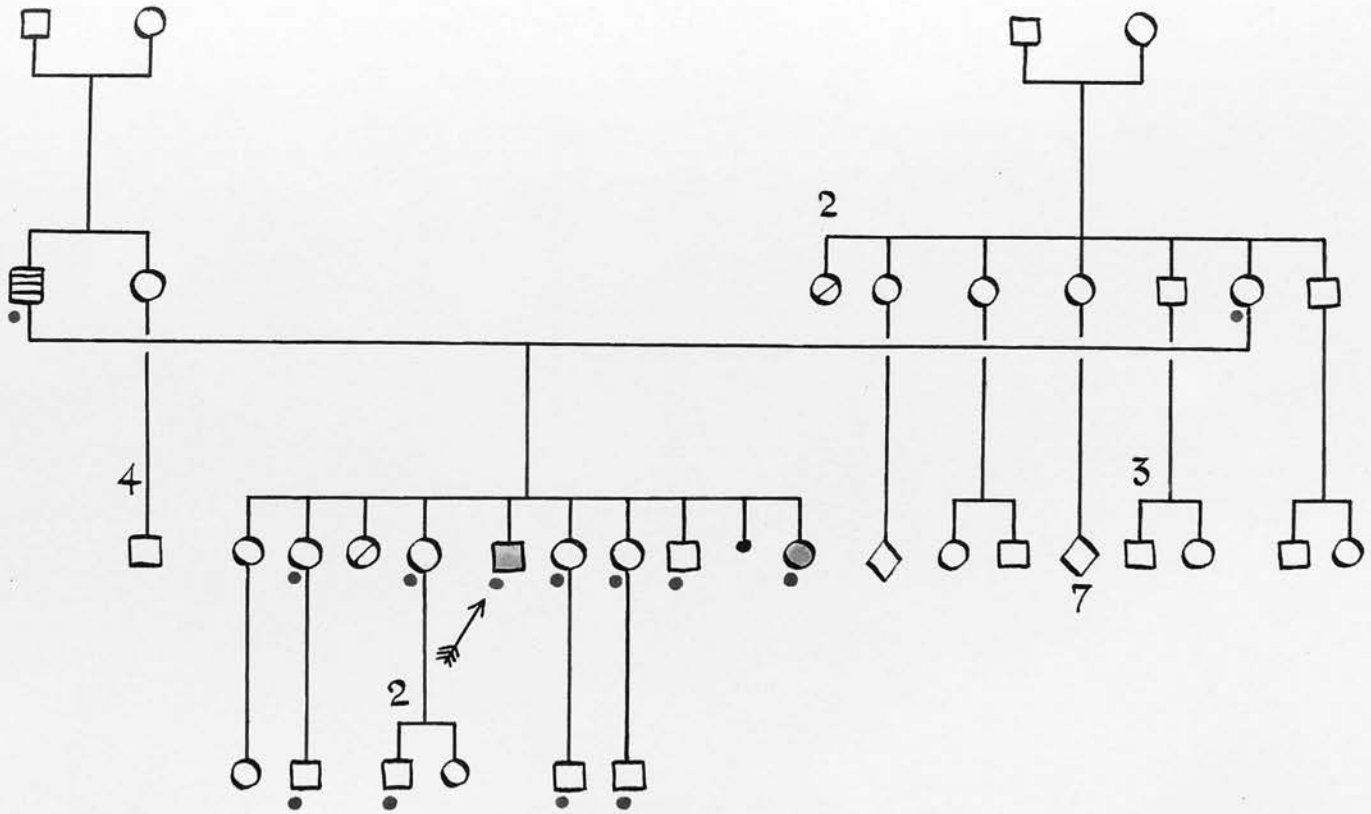
A sister is phenylketonuric.



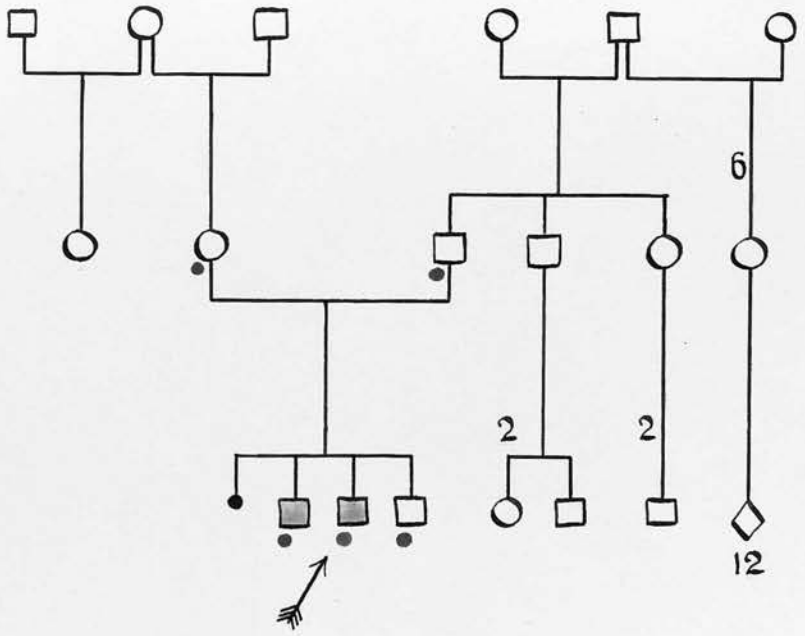
A grandmother shows senile amnesias.



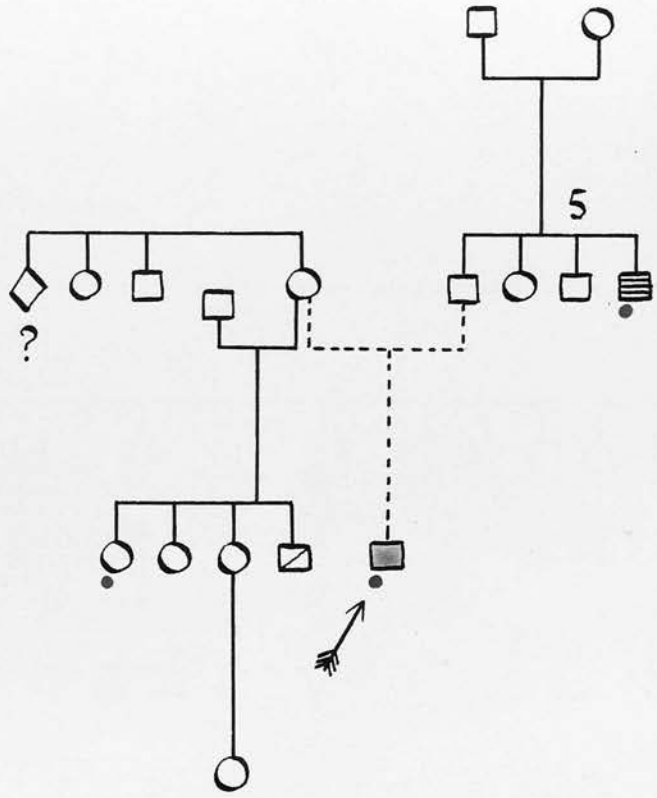
Two sibs died in infancy and another has phenylketonuria.
27 first cousins are well.



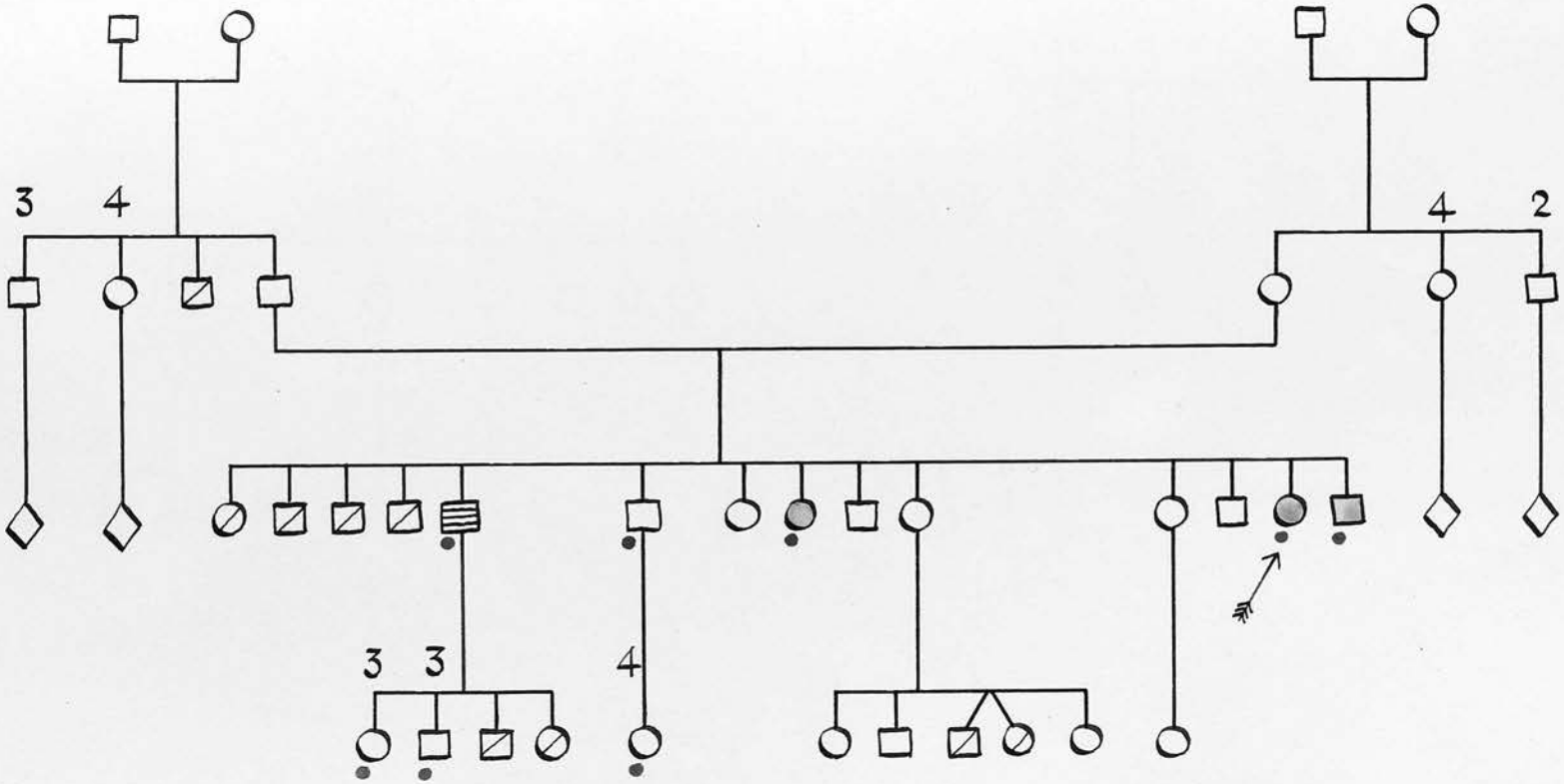
The father is mildly paranoid but well able to work.
One sister has phenylketonuria.



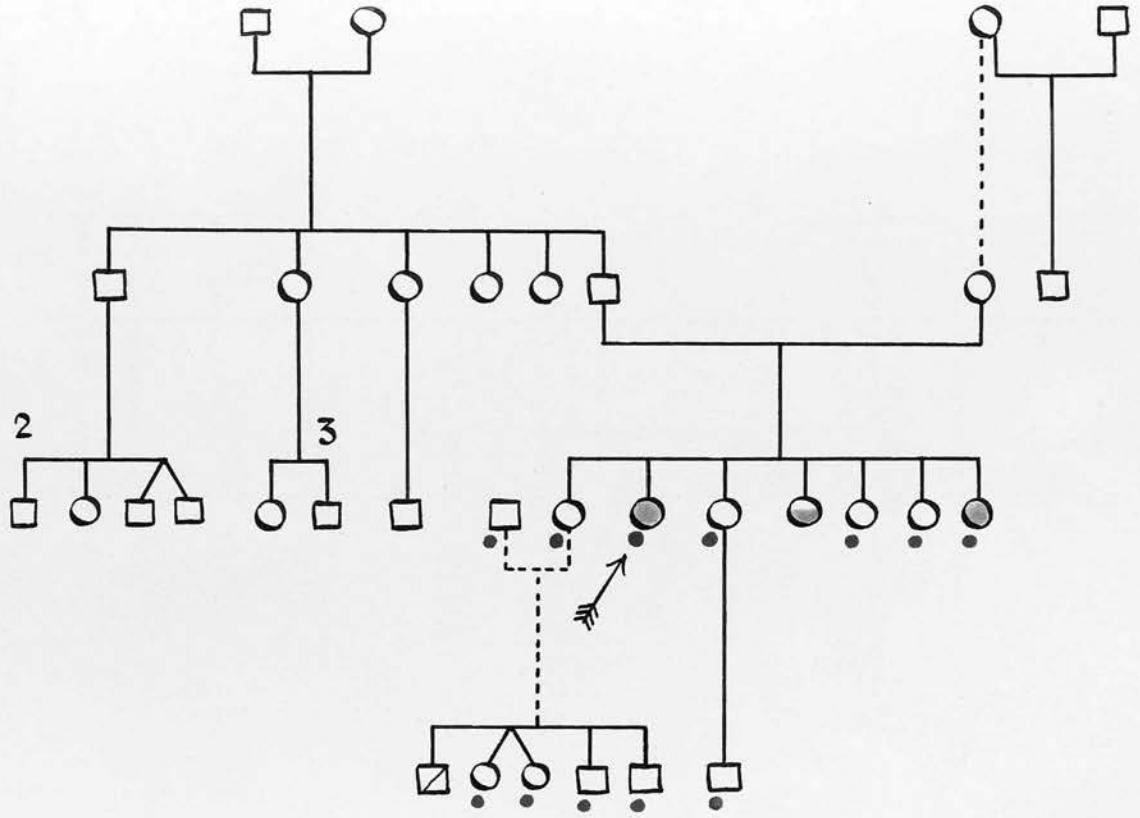
A brother has phenylketonuria.



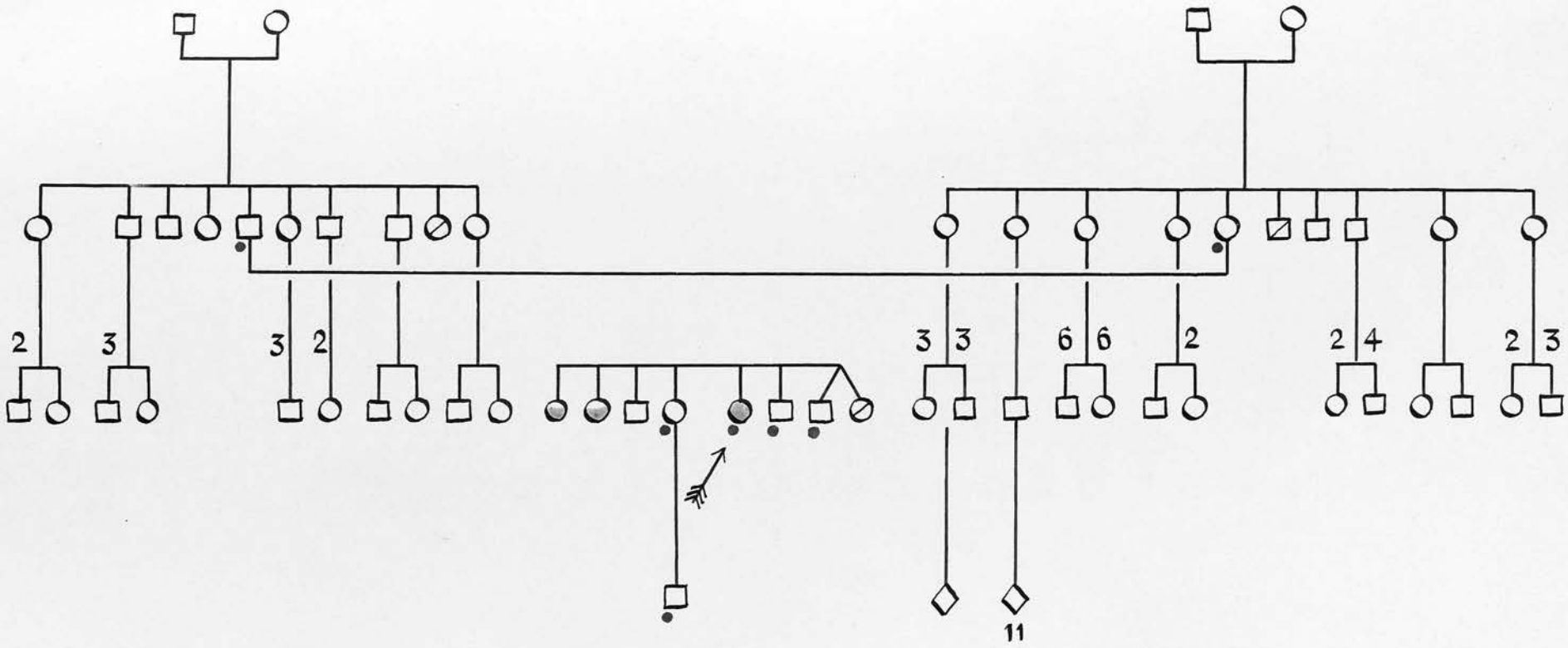
The propositus is illegitimate.
An uncle is a dullard.



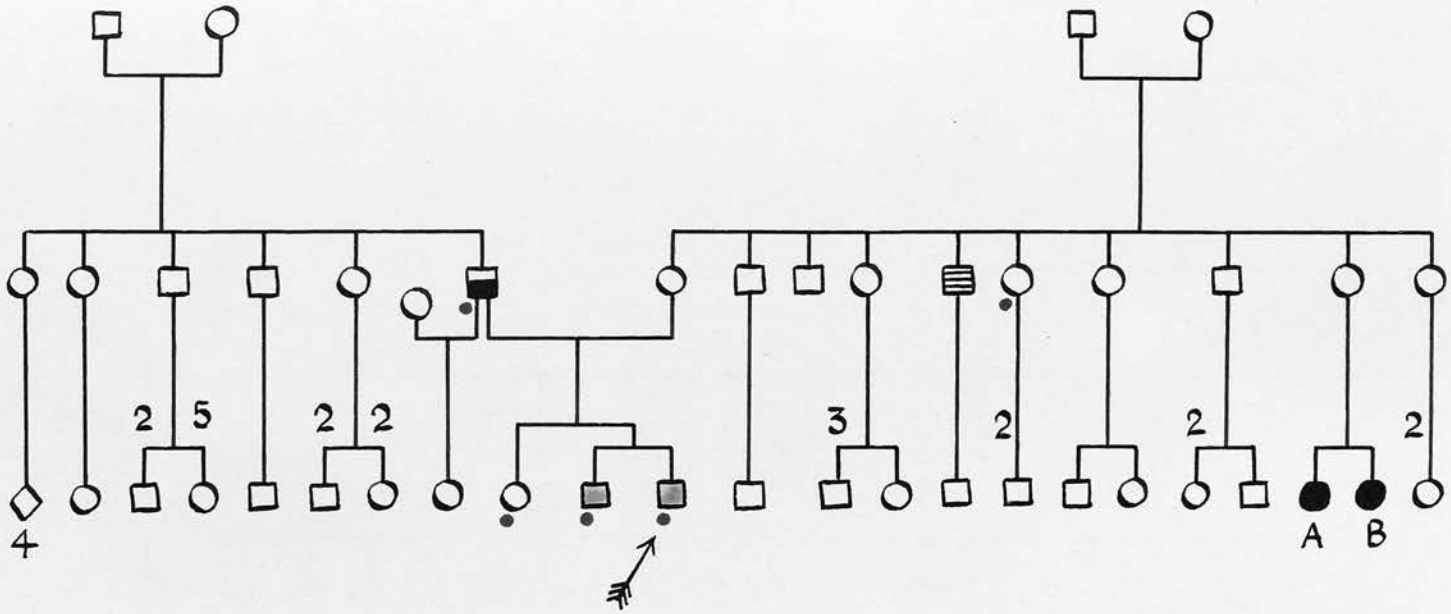
A sister and a brother have phenylketonuria, Another "brother" is a hypochondriacal epileptic of normal intelligence. His blood group proves that he cannot have had the same father as the other sibs.



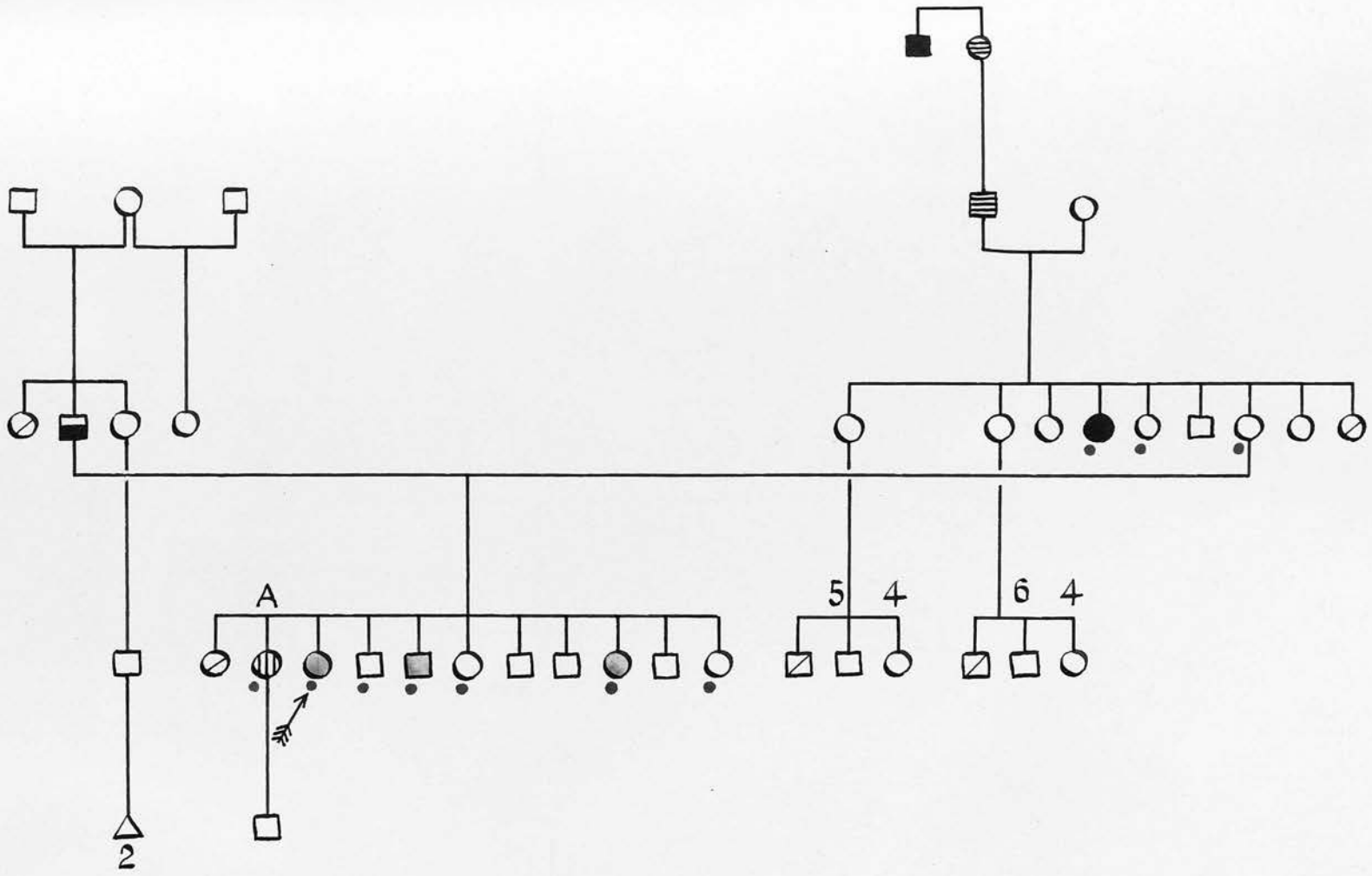
One sister is certainly and another was probably phenylketonuric.



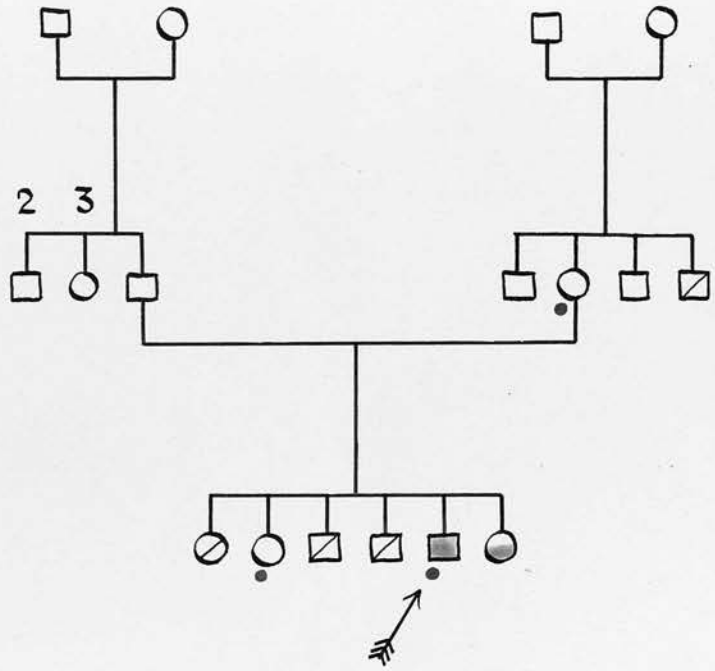
Two idiot sibs died in infancy, probable phenylketonuria.



The propositus is a monovular twin.
The father is a psychopath. A maternal uncle had a mental disorder and two cousins A and B, who died, were idiots of unknown type.

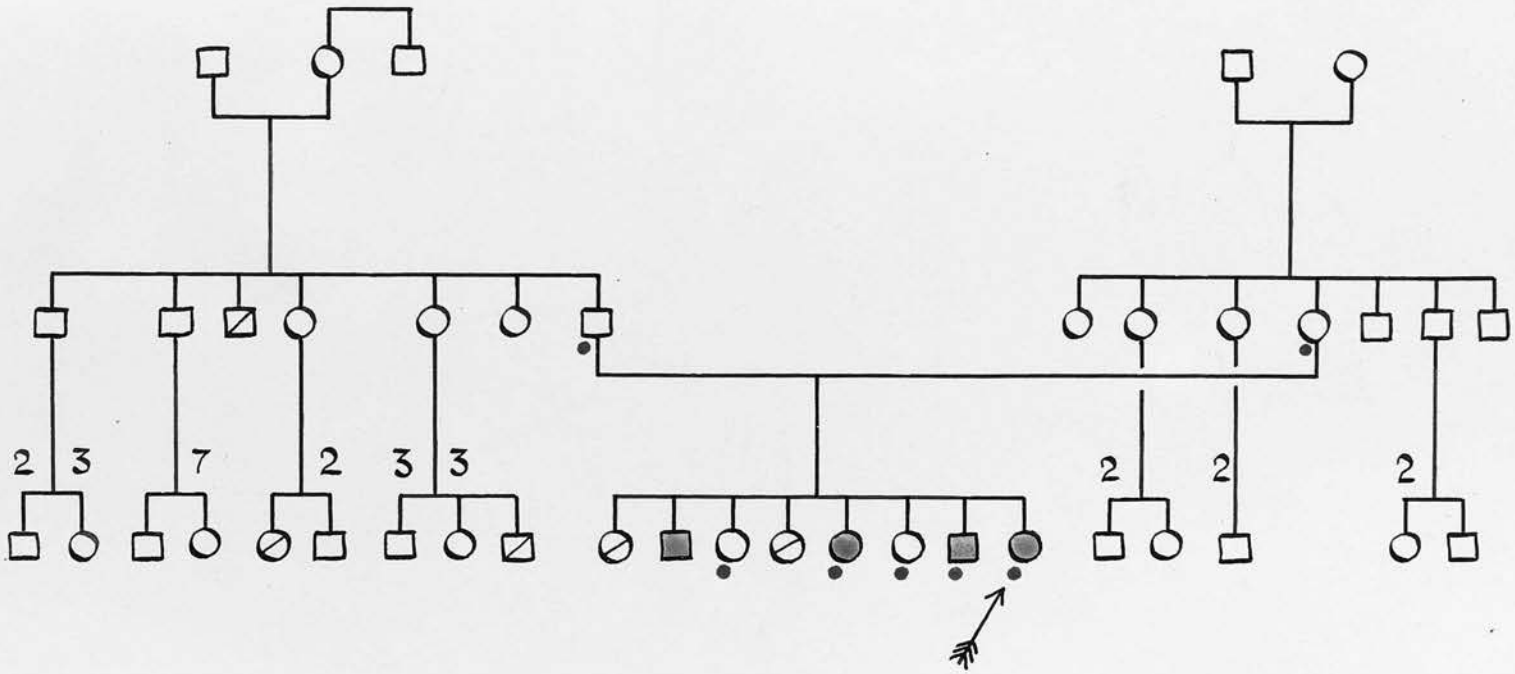


Two sibs are phenylketonuric and another, A, had hyperthyroidism. The father had a mild paranoid psychosis. A maternal aunt is an imbecile, not phenylketonuric, and the mother's father, grandmother and greatuncle were abnormal mentally.



An idiot sister died in infancy,
probable phenylketonuria.

The patient and his sister
were illegitimate twins.



Three sibs have phenylketonuria and another two died in infancy.
29 first cousins and also the other relatives are healthy.